METAL ION OXIDATIONS IN ORGANIC SYNTHESIS AND BIOMIMETIC REACTIONS

THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

VEENA MANCHANDA

DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH (INDIA)
1985-86

Dedicated
To My
Loving Parents

DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH, U.P., INDIA

PHONE-Office : 5515

Ref. No. _____

Date _____

This is to certify that the work discussed in the thesis entitled, 'METAL ION OXIDATIONS IN ORGANIC SYNTHESIS AND BIOMIMETIC REACTIONS', is the original work of the candidate and is suitable for the submission for the award of Ph.D. degree in Chemistry.

(Dr. N.U. Khan)
Supervisor.

ACKNOWLEDGEMENT

I express my deep sense of gratitude to Dr. Nizam-Ud-Din Khan, Lecturer, Department of Chemistry, Aligarh Muslim University, Aligarh, for his inspiring guidance and incessant encouragement throughout the course of this work.

I am highly indebted to Prof. W. Rahman, Ex-Head, Department of Chemistry, who has always been extending encouragements and inspirations. Thanks are also due to Prof. M.S. Ahmad, Chairman, Department of Chemistry, for generously providing the research facilities for the execution of the work.

A lot of appreciation goes to Dr. S. Mashhood Ali for his consistent help and co-operation in completion of the work. Dr. Jawed Iqbal and other laboratory colleagues are also thanked for their co-operative attitude.

I feel proud in putting in here a few words of appreciation for my loving parents, Er. Tushar Kapoor and Dr. Lalita Manchanda, for their affectionate ispirations without which the work could not have been accomplished.

Financial assistance from Council of Scientific and Industrial Research, New Delhi is highly acknowledged.

Veena Manchanda

(Veena Manchanda)

C O N T E N T S

****
****
****
*****
***
*

PART I

THEORETICAL

Living organisms are chemically reacting systems depending on the continuance of oxidations and reductions, for plants proliferate by using radiant energy to reduce carbon dioxide whilst animals obtain their vital energy by the oxidation of carbon compounds. Thus, the comprehension of mechanisms of oxidation and reduction processes is essential to the understanding of the nature of life and it is a task for the organic chemists to provide a clear picture of ways in which these chemical changes may take place with simple molecules, so that biologists can have a sure basis for their understanding of the behaviour of complex organisms.

Phenolic compounds are frequently found in plants. A variety of these phenolic compounds, found in higher plants and in microorganisms, can be derived formally from the oxidative coupling of phenolic compounds involving carbon-carbon and carbon-oxygen-linkages. The idea that phenol coupling is an important step in the biogenesis of different classes of natural products is strongly supported by the biochemical information using radioactive precursors[1a] which has established the intermediacy of substances predicted from phenol oxidation theory. Furthermore, synthetic experiments, based along this hypothetical biogenetic pathway, using oxidants known to promote one electron oxidation and hence ortho and para coupling of phenolic nuclei have resulted in the synthesis of a number of natural products[2,3], representative of a wide range of structural diversity.

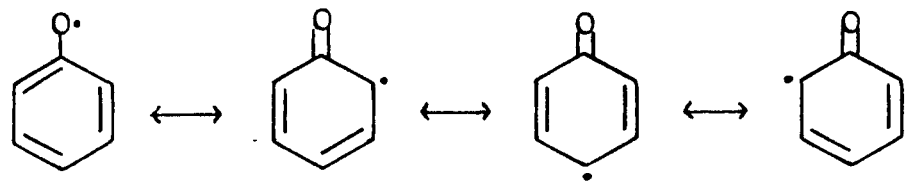
Much is known about the inhibition of autoxidation from technological than from theoretical aspects, for today all commercial petroleum products, rubber articles, most synthetic plastics and even certain foodstuffs are regularly treated, before sale, with small amounts of anti-oxidants. Phenols are of great industrial importance in the phenomenon of autoxidation, many commercially important anti-oxidants being phenols[4a]. Phenols are oxidized with oxygen and air in neutral and alkaline solutions with and without different catalysts or radical initiators[4b] to generate phenoxy radicals and it is on account of the stability, and therefore low reactivity of such radicals that phenols are potent inhibitors of autoxidation. Alkyl groups decrease the electron spin density associated with the aromatic ring and alkylated phenols are more readily oxidized to radicals than is phenol itself. The most effective type of anti-oxidants are highly alkylated or hindered phenols. In an attempt to assess the possible toxicity of phenolic anti-oxidants for use in food, their oxidation products became important because in preventing autoxidation of a substance a phenol is itself oxidized, generally to a variety of compounds which may, therefore, be ingested.

Intensive research on the oxidation of phenols has been carried out to prove that phenol coupling occurs in vivo[5]. The subject is still of growing importance as an important synthetic tool and in biosynthetic schemes for many natural products[6,7].

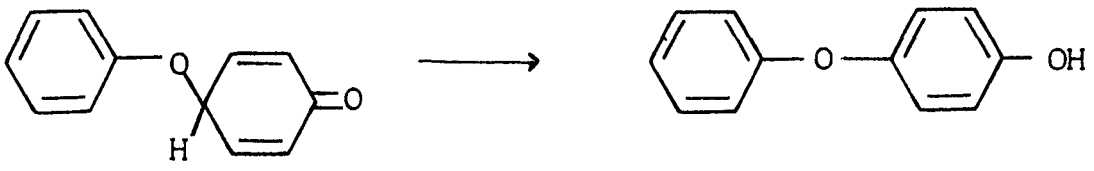
Transition metal ions occupy a central place in the organic chemist's arsenal of oxidants. They are for the most part stable, inexpensive reagents that are easily stored and handled. Because of these desirable properties, transition metal oxidants have been extensively employed in synthetic organic chemistry. Considerable selectivity with respect to functional groups and stereochemistry can be achieved by choice of the proper oxidant and proper conditions. However, when the highest yields of dimeric coupling products are desired, only a few are to be considered. Potassium ferricyanide in alkaline solution has often been found to be very effective, particularly, when using a two phase system of an aqueous alkaline layer with chloroform, benzene and ether etc. Ferric chloride in neutral or acidic solution or adsorbed on silica gel has also been extensively used. There is, however, at present no way to predict which method might be the best for any particular case of phenol coupling. If a close analogy is available in the literature and high yields are reported, these would obviously be tried first. It is only realistic to mention, however, that phenol coupling may be very difficult to achieve, and there are many examples of this in simple and in more complex molecules[1b].

MECHANISM OF PHENOL OXIDATION

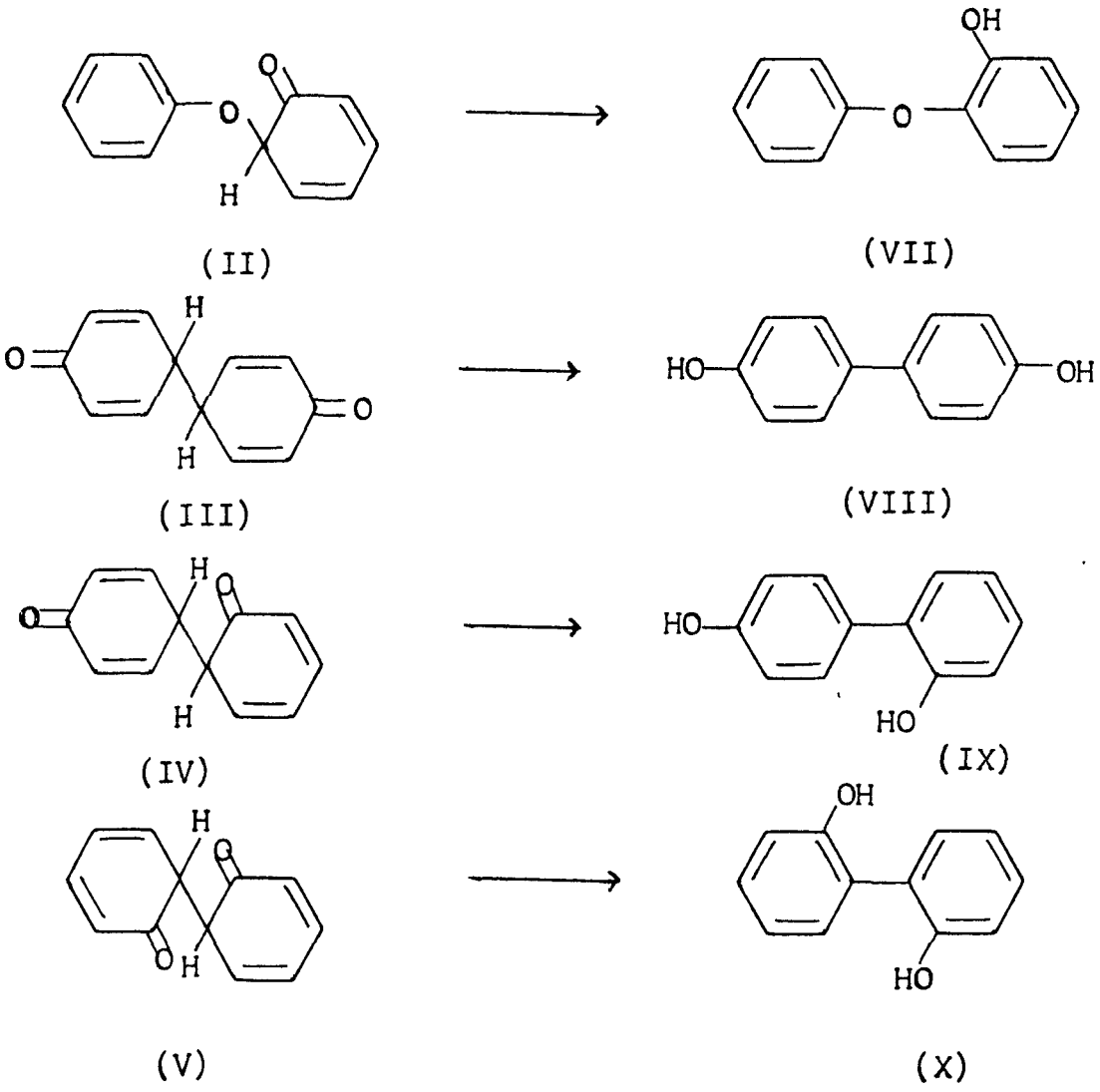
Towards one-electron oxidants phenols react either by the loss of hydrogen atom of the hydroxyl group or by loss of one electron from the corresponding anion to give free aryloxy radicals. These radicals are stabilized by resonance, and the odd electron is distributed over the oxygen atom and all carbon atoms of the aromatic ring. The highest spin density is found on oxygen and at the p-position.



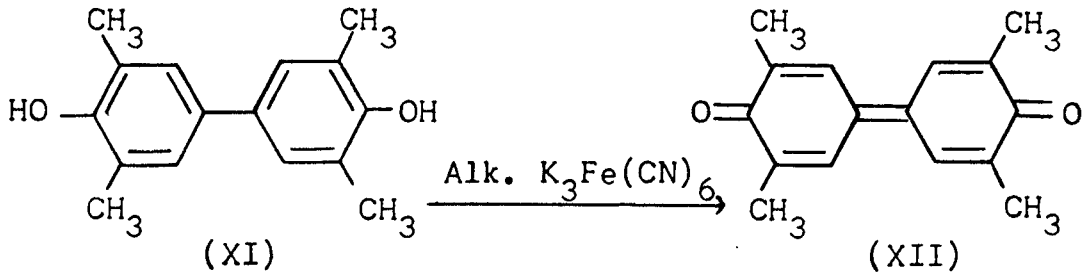
Ultimately, complex mixtures result from the coupling of these radicals. The simplest products that can be formed by coupling, either through oxygen or through carbon atoms, are dimers (I-V) which should tautomerize rapidly in protic solvents to the stable aromatic products (VI-X).



(I) (VI)

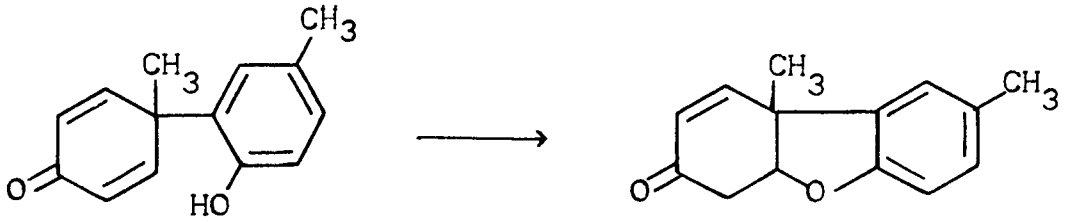


The formation of trimeric and polymeric compounds can be formulated in the same way. If the oxidation potential of the oxidizing agent is high enough the C-C-coupled dimers can be oxidized further to extended quinones. For example, oxidation of 2,6-xylenol with alkaline potassium ferricyanide gave para-para coupled dimer (XI) which was further oxidized to diphenoquinone (XII)[8].



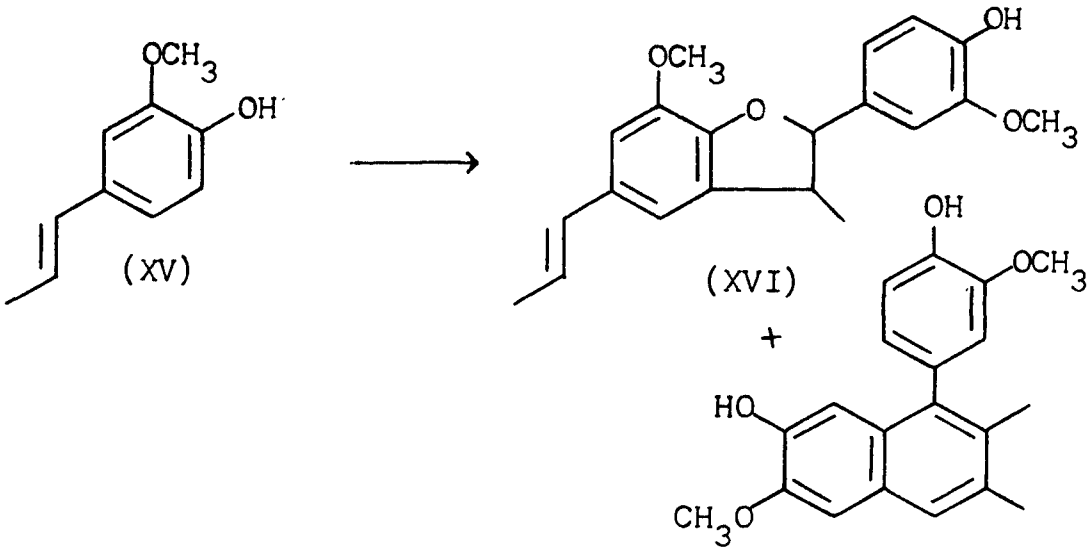
(XI) (XII)

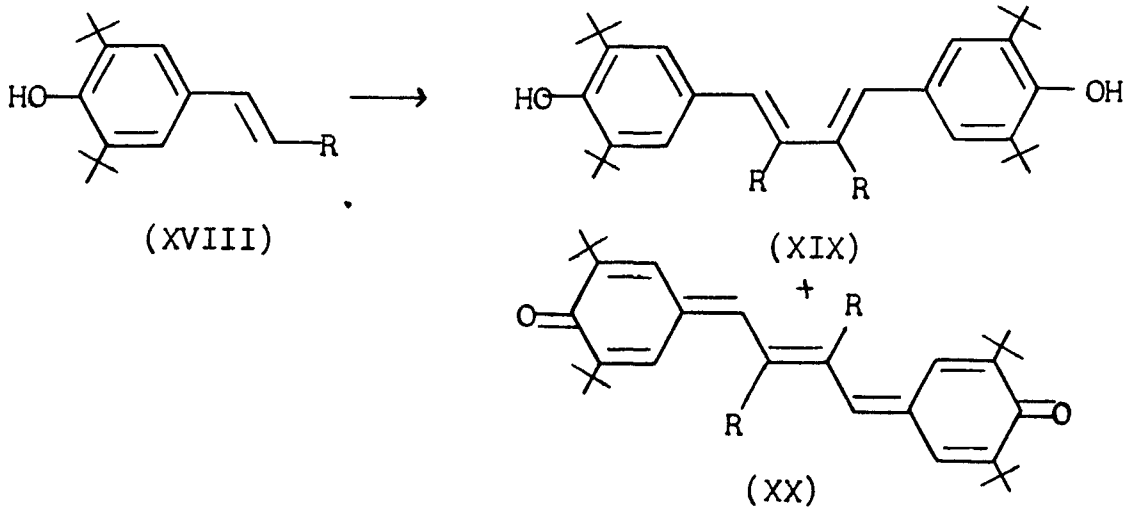
In the case of phenols with a para substituent, for example, p-cresol, Pummerer's ketones (XIV), which are formed by the rearrangement of XIII, are sometimes obtained[9].



(XIII) (XIV)

Conjugated side chains can be involved in phenol coupling, for example, the propenyl group of 2-methoxy-4-propenylphenol (XV) in the formation of XVI and XVII[10]. In the case where all three, two ortho and one para, positions are substituted by bulky or inert groups, the free phenoxy radicals are more or less stable. In the case of 2,6-di-t-butyl-4-vinylphenol (XVIII), the p-vinyl groups, however, undergo dimerization at the β-positions to give products XIX and XX[11].

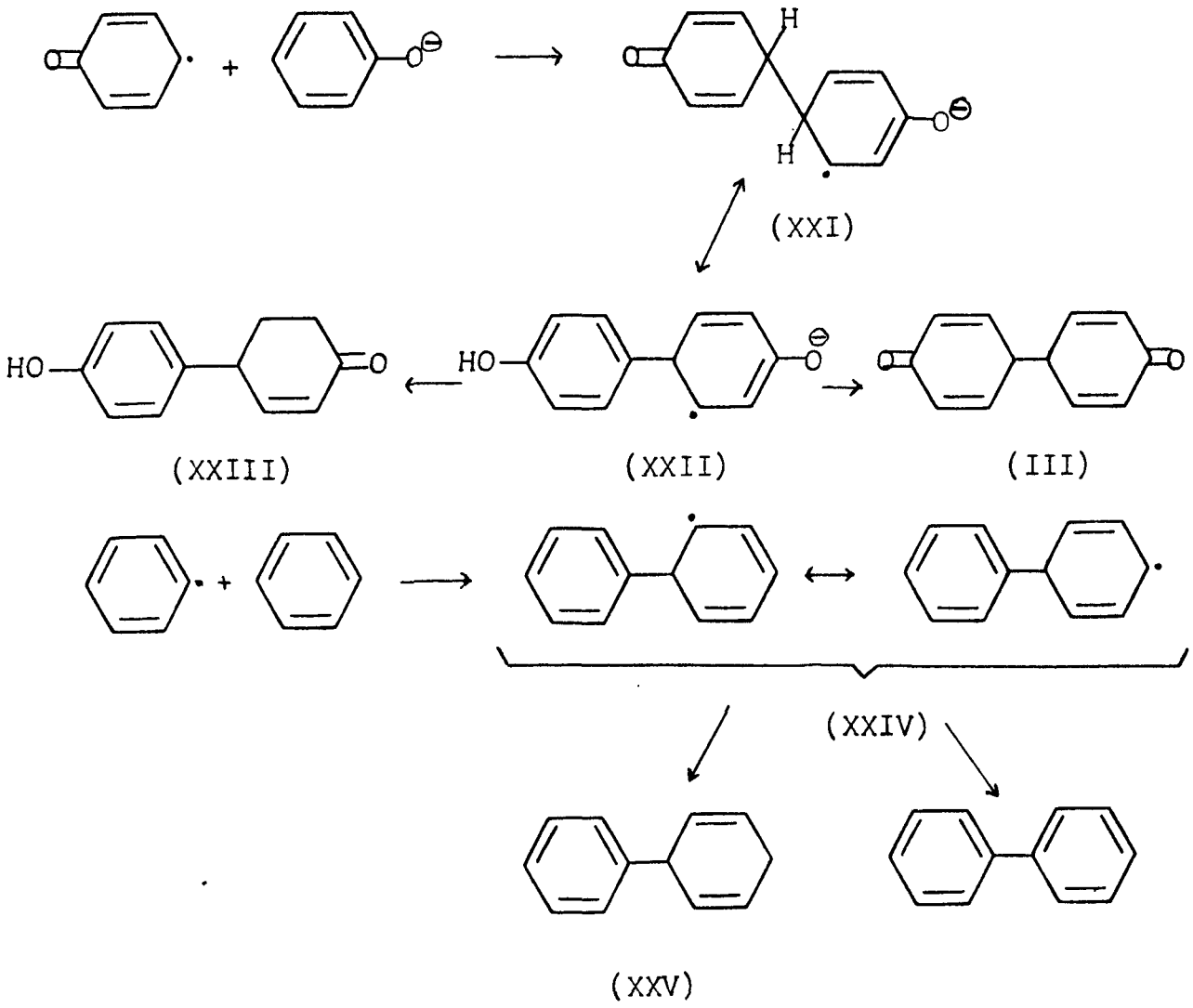


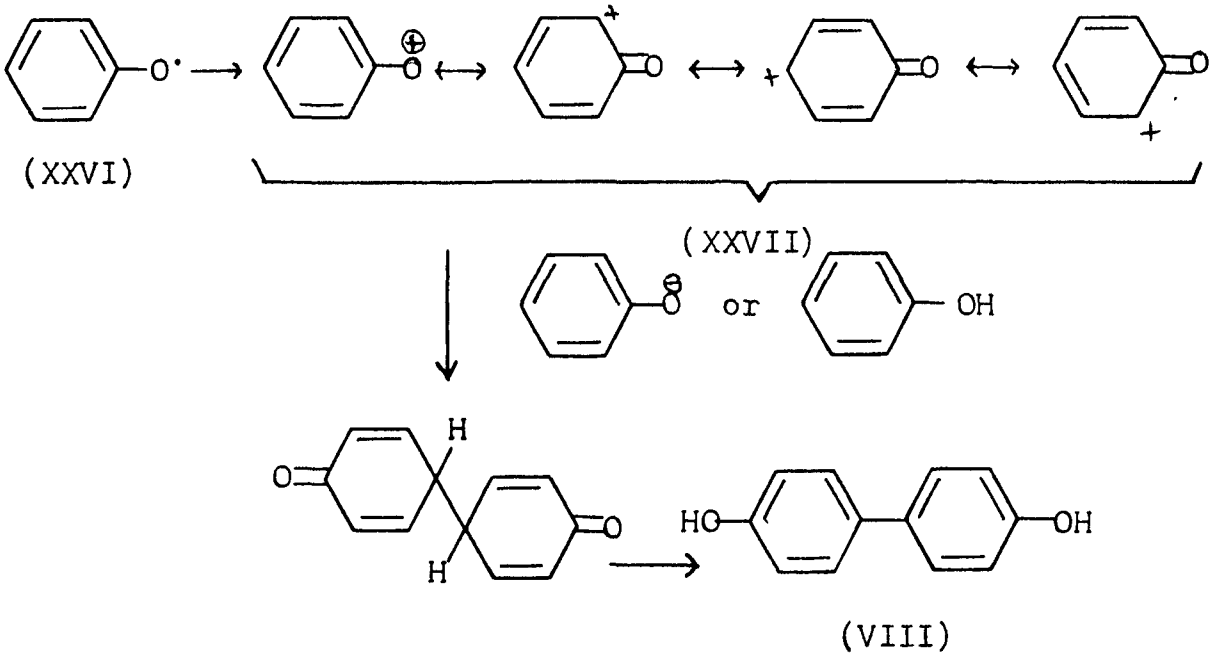


There are also two other possible mechanisms (Scheme I). First, the free phenoxy radical attacks a phenol or phenolate anion leading to a dimeric radical XXI or XXII, which is in turn oxidized further to give III. The dimer radicals could abstract a hydrogen atom from some donar to yield a dihydro product XXIII. Such compounds, for example XXV[12], have been observed in free radical

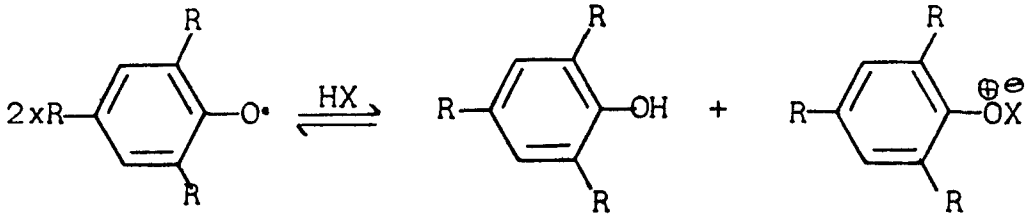
aromatic substitution, but they have never been isolated in phenol oxidations. Obviously, however, there is no evidence against such a mechanism. Second, the free phenoxy radical (XXVI) is oxidized further to a cation XXVII, which should react rapidly with a phenol or a phenolate anion to afford dimer VIII.

Scheme I





The disproportionation of two stable radicals with a strong acid in aprotic solvents to give one phenol (XXVIII) and one phenoxy cation salt (XXIX) has been reported[13].



Many features of phenol oxidation are not yet fully understood[4c]. For instance, the oxidation of any monohydric phenol by alkaline ferricyanide, or a similar reagent, usually produces far more polymeric than dimeric material and it is not yet clear

why this polymer should so easily be formed. The polymers often appear to have chains of aromatic nuclei linked through oxygen and clearly are not formed by the stepwise oxidation of the dimeric molecules instanced above. In fact trimers are formed from many phenols in surprisingly good yields. Radical addition to phenol molecules, or phenolic anions has been suggested tentatively and it has been shown how polymerization might be effected by a combination of homolytic and heterolytic reactions. At present, however, the best theory for the phenol coupling mechanism is that the phenolate anion is oxidized by the reagent to a free phenoxy radical. These are then coupled rapidly and irreversibly to dimeric and polymeric products under kinetic control. It is reasonable to assume that the coupling occurs fastest at the positions of highest density of the free electron, except where there is steric hinderance to approach.

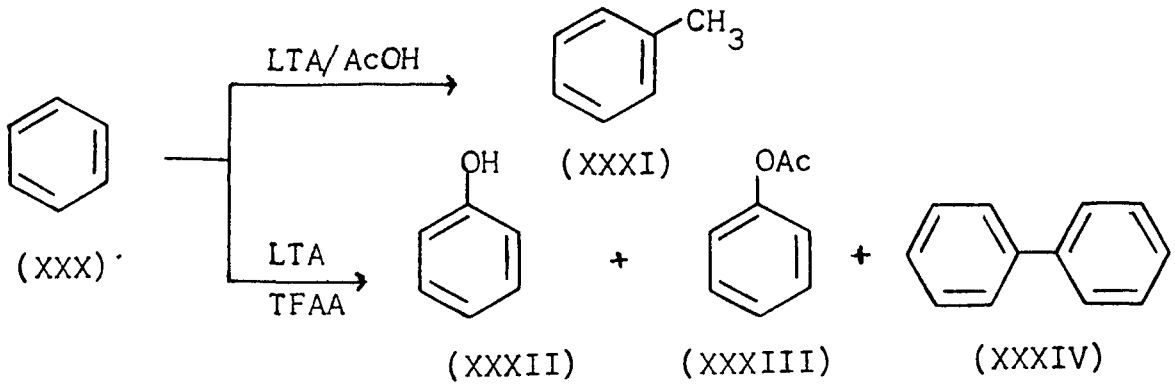
METAL-ION OXIDATION

Most effective metal salt catalysis depends both on the chemical nature of the organic compound, which is being oxidized, and on operational temperature. Depending on the structure of the metal compounds and ionization potential of the aromatic compounds, metal-ion oxidation can be classified into following categories. Electron transfer between the organic compound and the metal ion[14-17], radical reaction initiated by decomposition of a metal

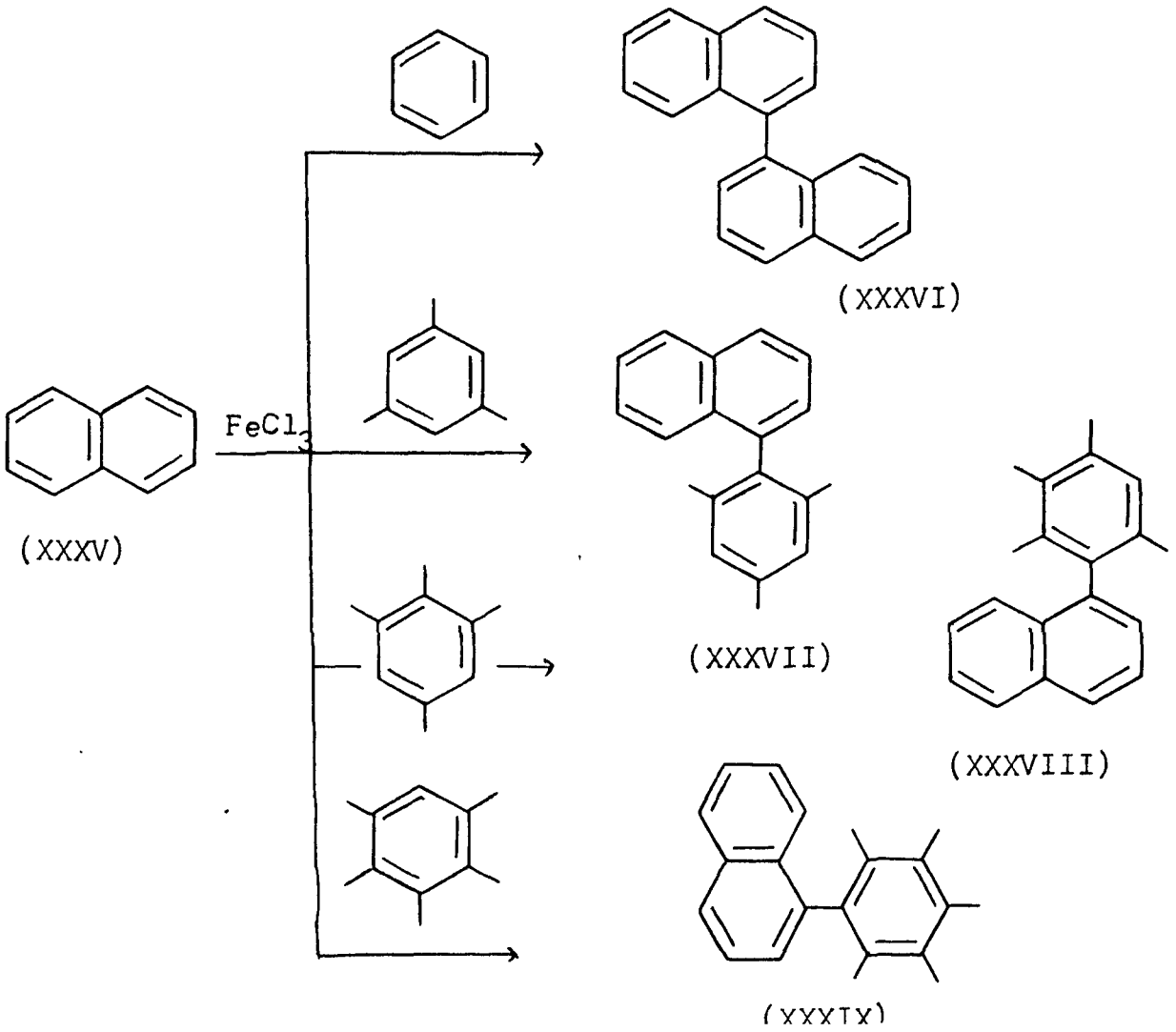
salt[18-21], electrophilic reaction between an aromatic compound and a metal salt[22] and reaction within the co-ordination sphere of the metal complex[23]. As a consequence of the great popularity of the metal-ion oxidation, it is impossible within the confines of this thesis to give detailed description of all the ways in which they have been employed. Instead, an attempt has been made to indicate the products that are likely to result from the oxidation of aromatic hydrocarbons, phenols, alkoxy phenols with metal-ion oxidants under various conditions.

METAL-ION OXIDATION OF AROMATIC HYDROCARBONS

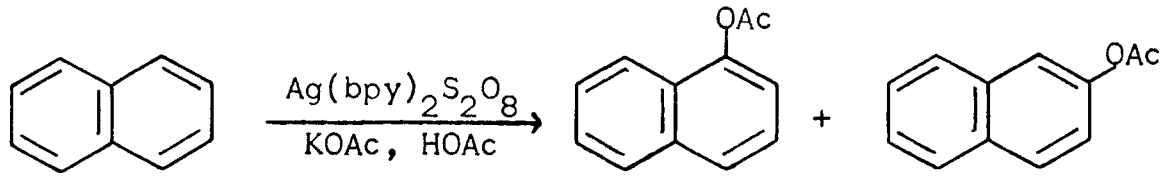
The reaction of benzene (XXX) with lead tetra acetate (LTA) in acetic acid at reflux temperature gave toluene (XXXI)[24]. But LTA oxidation of benzene in presence of trifluoro- or trichloroacetic acid afforded phenol (XXXII), aryl acetate (XXXIII) and biaryl (XXXIV)[18]. However, the aerial oxidation of benzene to phenol proceeds under ambient condition only when Cu^{+} ions are present in solution[25].



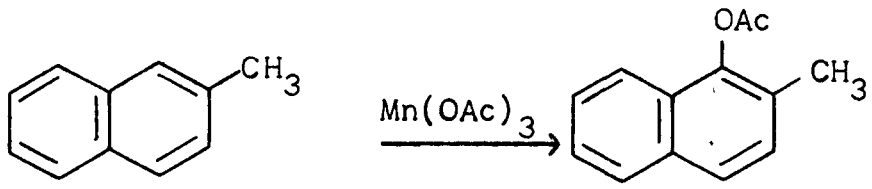
Nyberg[26] has accomplished the synthesis of unsymmetrical biphenyls (XXXVI-XXXIX) by the oxidation of naphthalene (XXXV) with ferric chloride. Thus, oxidation of XXXV in the presence of benzene afforded binaphthyl (XXXVI). While 1-aryl naphthalenes (XXXVII-XXXIX), formed by the intermolecular coupling of naphthalene and polymethylbenzenes, were obtained when the reactions were carried out in the presence of mesitylene, isodurene and pentamethylbenzene, respectively. Product XXXVII has also been prepared by the Co(III) and Mn(III) acetate oxidation of XXXV in the presence of mesitylene.[27]



Naphthalene undergoes oxidative acetoxylation in the presence of Ag(II) complex, potassium acetate and acetic acid to give 1-acetoxynaphthalene (XL) and 2-acetoxynaphthalene (XLI)[28]. Oxidation of 2-methylnaphthalene (XLII) with Mn(III) acetate also affords oxidative acetoxylated product, 1-acetoxy-2-methylnaphthalene (XLIII)[18].

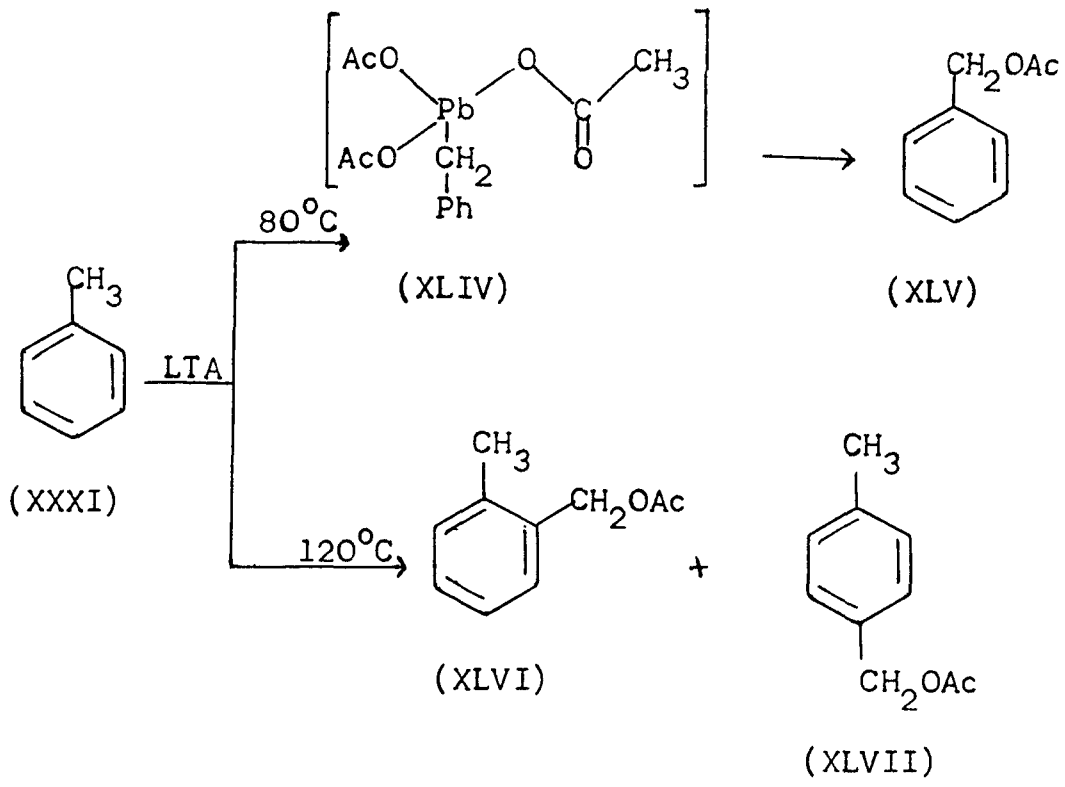


(XXXV) (XL) (XLI)

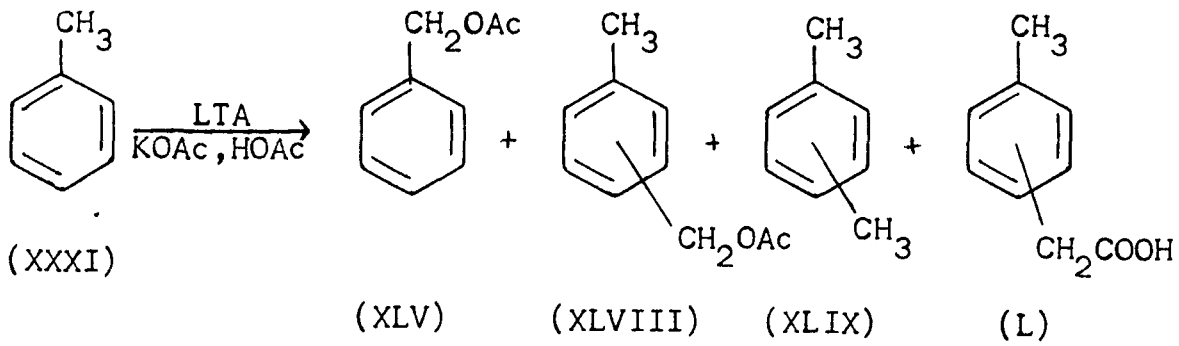


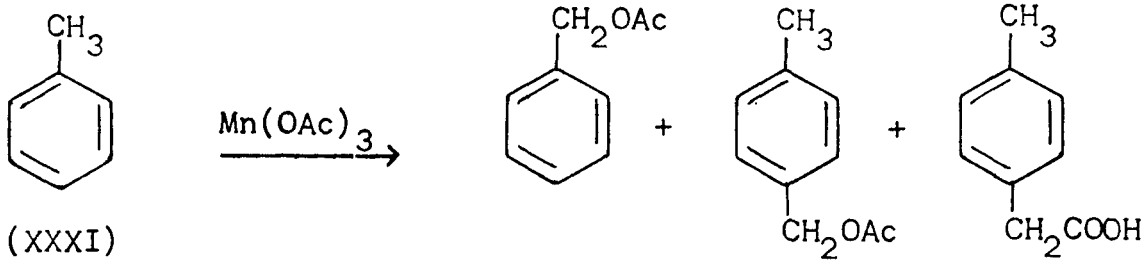
(XLII) (XLIII)

Lead tetra acetate (LTA) oxidation of toluene (XXXI) has been carried out under various conditions. Oxidation of toluene at 80°C afforded benzyl acetate (XLV) and no dibenzyl was obtained. The absence of dibenzyl as the product suggested that free benzyl radical was not present and complex intermediate (XLIV) was, probably, formed which decomposed to give benzyl acetate. When the reaction was carried out at 120°C, o- and p-methylbenzyl acetates (XLVI) and (XLVII) were obtained which may be formed by the methylation of benzyl acetate with free methyl radical[24].



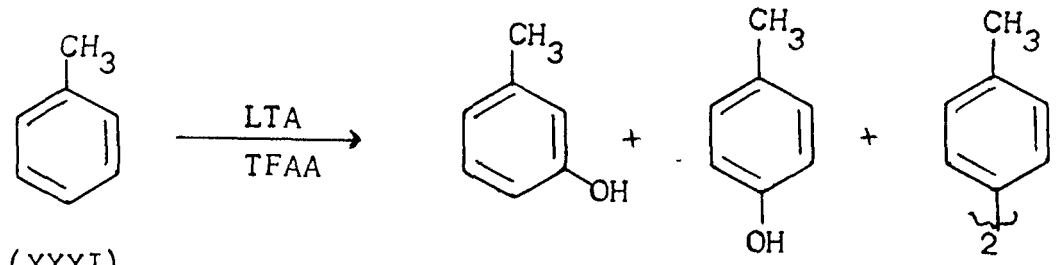
But LTA oxidation of toluene (XXXI) in refluxing acetic acid containing anhydrous potassium acetate under nitrogen atmosphere yielded two major products, benzyl acetate (XLV) and methyl benzyl acetate (XLVIII) alongwith minor amounts of xylene (XLIX) and tolylacetic acid (L)[21]. Acetates XLV and XLVIII were also obtained alongwith p-tolylacetic acid (LI) by Mn(III) acetate oxidation of toluene[17].





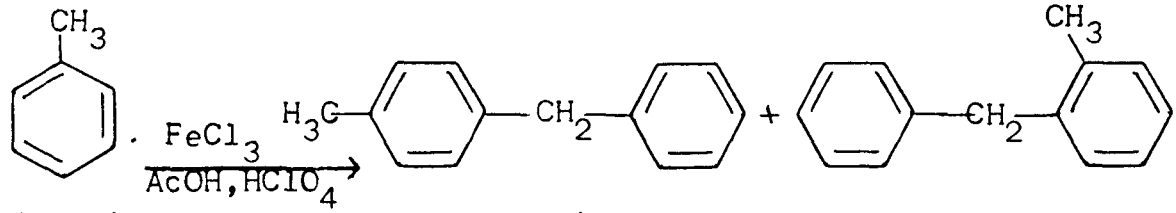
(XXXI) (XLV) (XLVIII) (LI)

When toluene was oxidized by LTA in TFAA, an exothermic reaction took place which on hydrolytic work up gave m-cresol (LII), p-cresol (LIII) and bitolyl (LIV)[18].

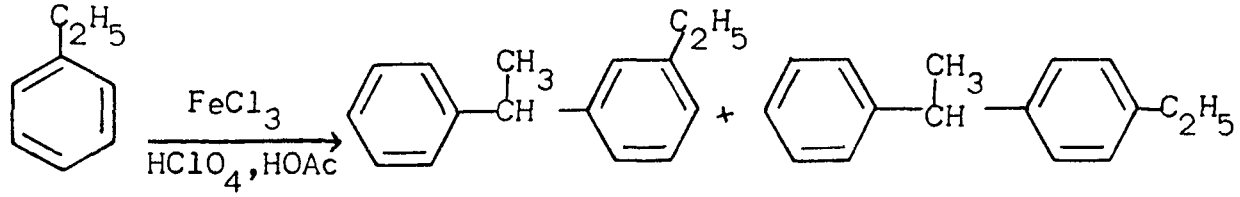


(XXXI) (LII) (LIII) (LIV)

However, toluene on oxidation with Fe(III) chloride in presence of strong acid, such as perchloric acid and acetic acid, gave diarylmethanes, LV and LVI. Ethyl benzene (LVII) also forms diarylmethanes, LVIII and LIX, on oxidation with ferric chloride in acetic acid in the presence of perchloric acid[29].

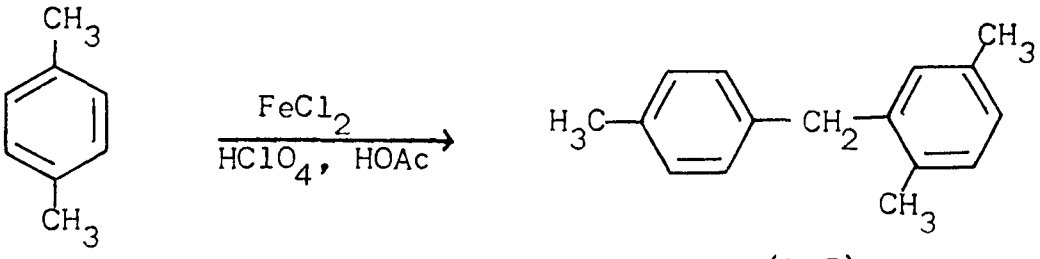


(XXXI) (LV) (LVI)



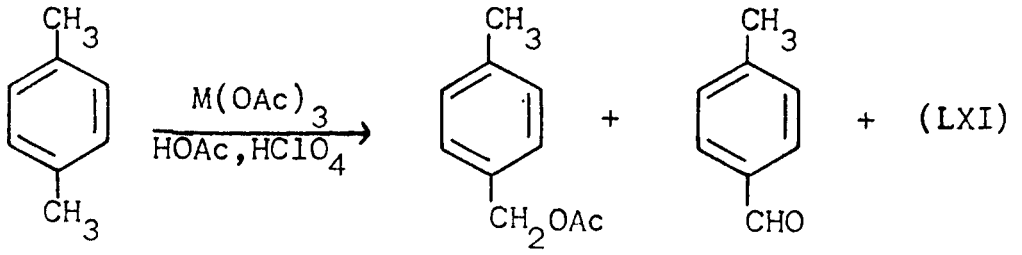
(LVII) (LVIII) (LIX)

The dehydrodimerization of p-xylene (LX) with iron(II) chloride and perchloric acid in acetic acid yields diarylmethane (LXI). The yield is better than 100% if one assumes that iron(III) species, formed by the oxidation of iron(II) with perchloric acid, is the oxidant responsible for converting LX into LXI[30]. Compound (LXI) has also been obtained by the oxidation of LX with Fe(III) chloride in acetic acid in the presence of perchloric acid[29].



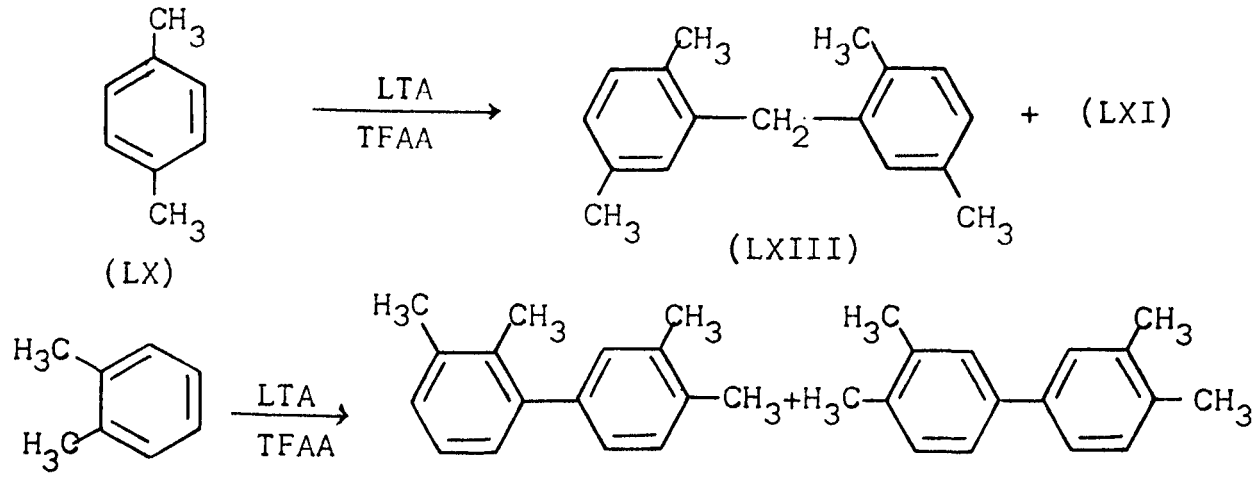
(LX) (LXI)

Treatment of alkylbenzenes with various metal acetates [Mn(III), Fe(III), Co(III) and Pb(IV)] in acetic acid containing perchloric acid at reflux temperature affords diarylmethanes as the main products. Thus, oxidation of p-xylene (LX) with these metal acetates yielded diarylmethane (LXI) as the main product alongwith minor amounts of p-methylbenzyl acetate (XLVII) and p-tolualdehyde (LXII)[31].

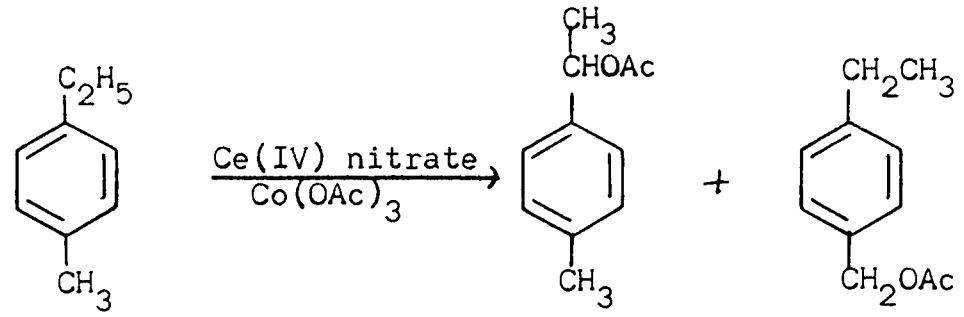


(LX) (XLVII) (LXII)

LTA oxidation of p-xylene (LX) in presence of trifluoroacetic acid at low temperature gave only diarylmethanes, LXI and LXIII. Under similar reaction conditions o-xylene (LXIV) afforded biphenyls, LXV and LXVI, and no diarylmethanes were obtained[32].

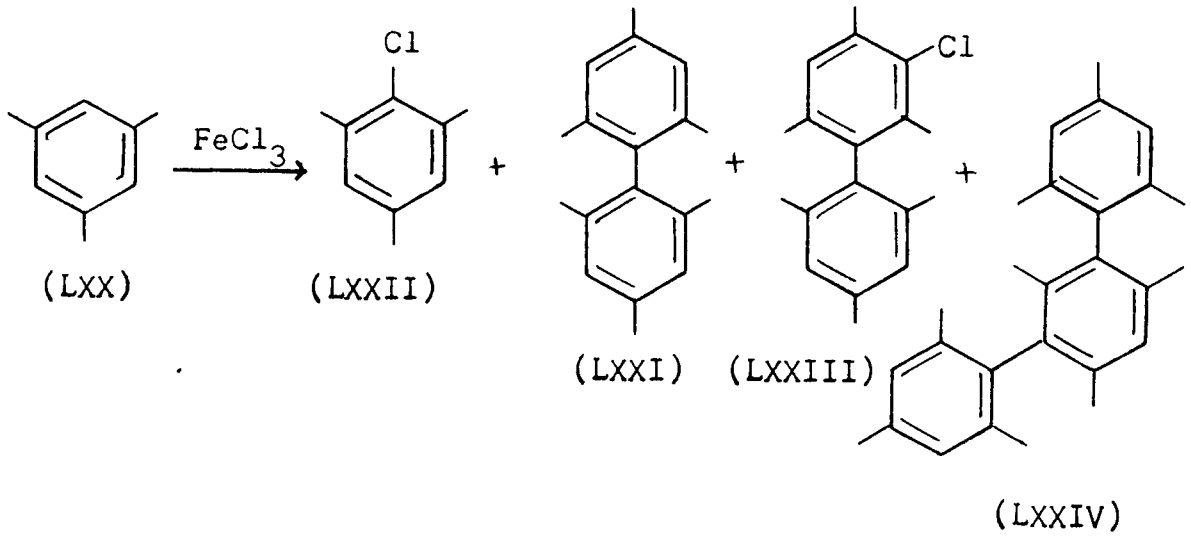


Enrico and Luigi[33] have reported intramolecular selectivity in the side chain oxidation of p-ethyltoluene (LXVII) with Co(III), Ce(IV) and Mn(III) salts. In the reaction of LXVII with these oxidants, benzyl acetates LXVIII and LXIX were obtained.



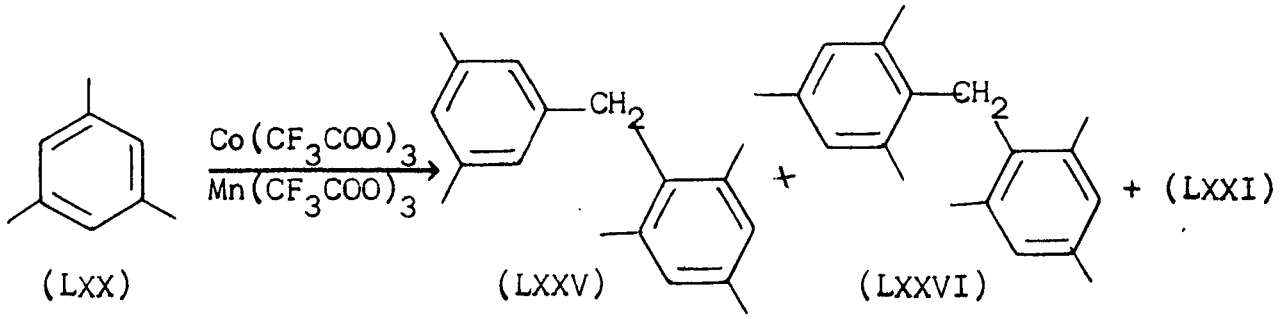
(LXVII) (LXVIII) (LXIX)

Oxidation of mesitylene (LXX) with iron(III) chloride produces bimesityl (LXXI) alongwith minor amounts of 2-chloromesitylene (LXXII), chlorobimesityl (LXXIII) and termesityl (LXXIV)[34]. When cobalt(III) and manganese(III) trifluoroacetates were used as oxidants and trifluoroacetic acid as medium, mesitylene afforded three products, 2,4,6,2',4',6'-hexamethylbiphenyl (LXXI), 2,4,6,3',5'-pentamethyldiphenylmethane (LXXV) and 2,4,6,2',4',6'-hexamethyldiphenylmethane (LXXVI)[27]. Products LXXI and LXXV were also obtained by LTA oxidation of mesitylene in TFAA[32].



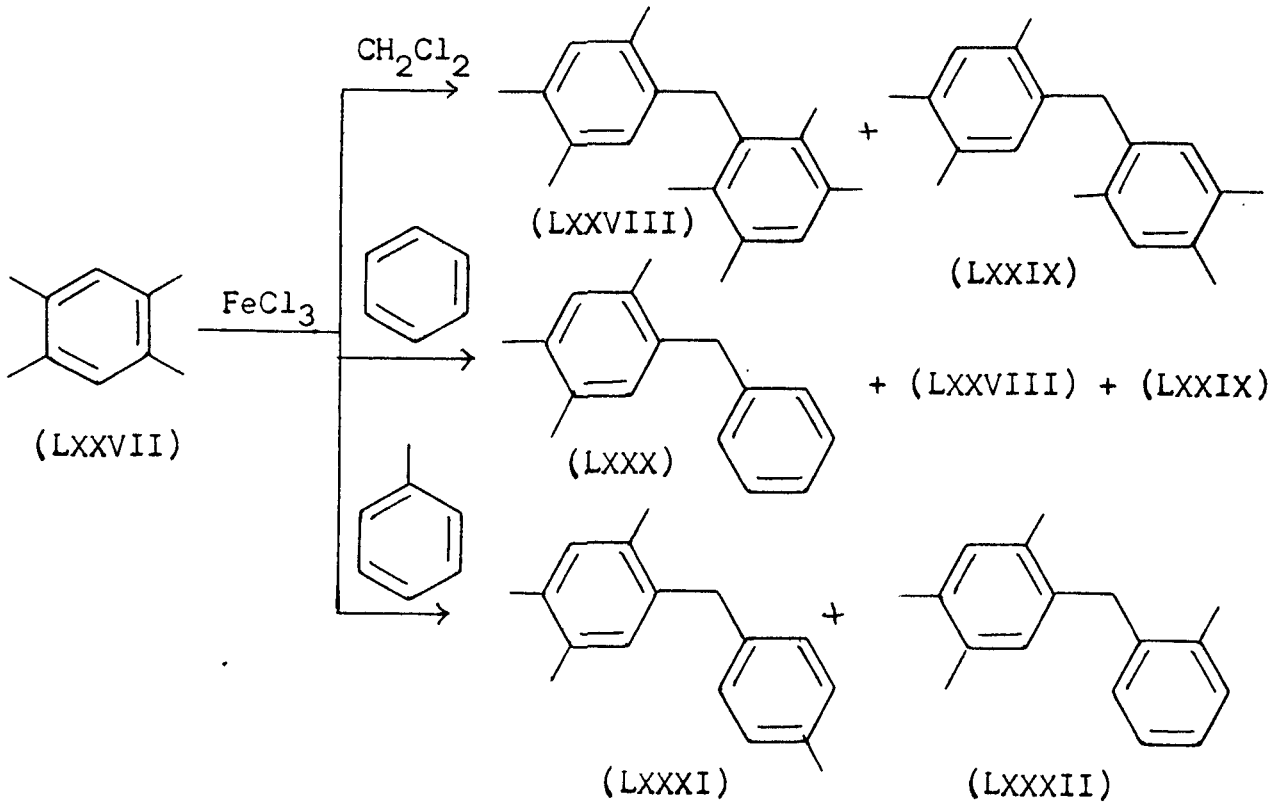
(LXX) (LXXII) (LXXI) (LXXIII)

(LXXIV)

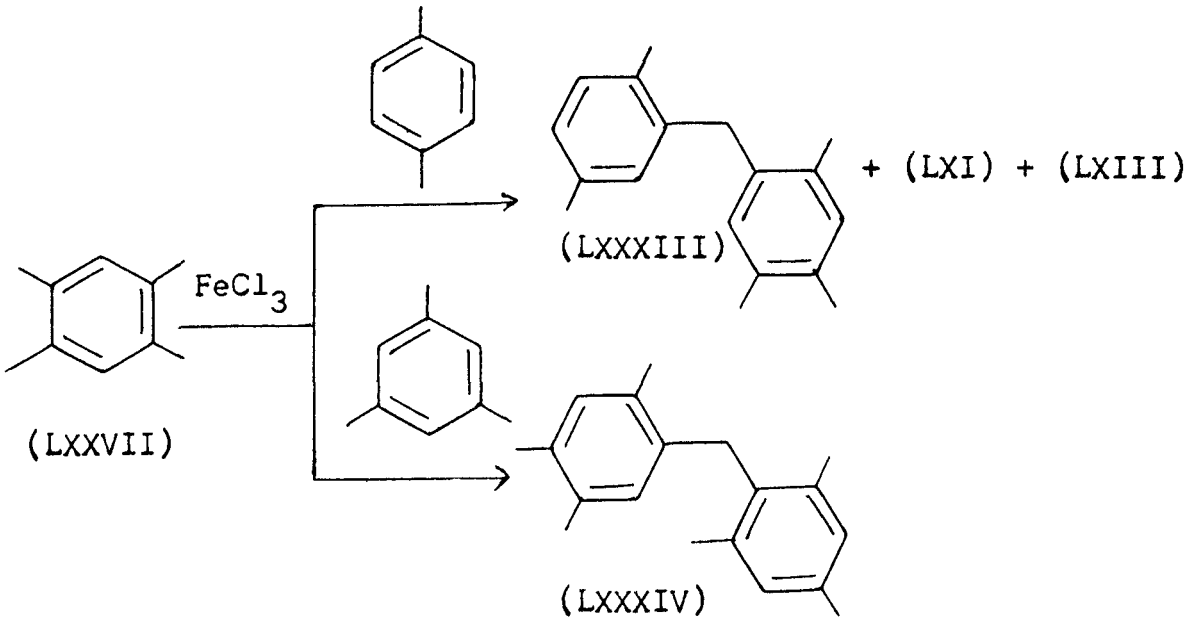


(LXX) (LXXV) (LXXVI)

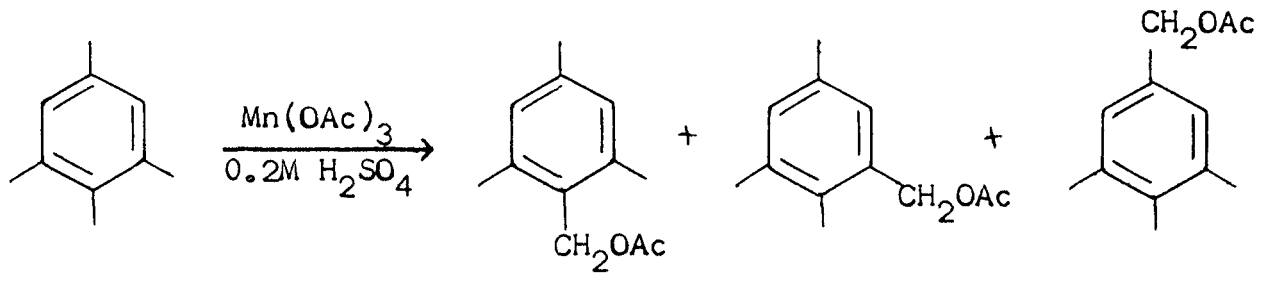
Nyberg[34] has studied the oxidation of durene (LXXVII) with ferric chloride in the presence of different solvents. Oxidation of durene in dichloromethane afforded diarylmethanes LXXVIII and LXXIX, while oxidation in the presence of benzene yielded diarylmethane (LXXX) alongwith minor amounts of LXXVIII and LXXIX. No dehydrodimer of durene was obtained when the oxidation was carried out in the presence of toluene, p-xylene and mesitylene.



(LXXVII) (LXXVIII) (LXXIX) (LXXX) (LXXXI) (LXXXII)



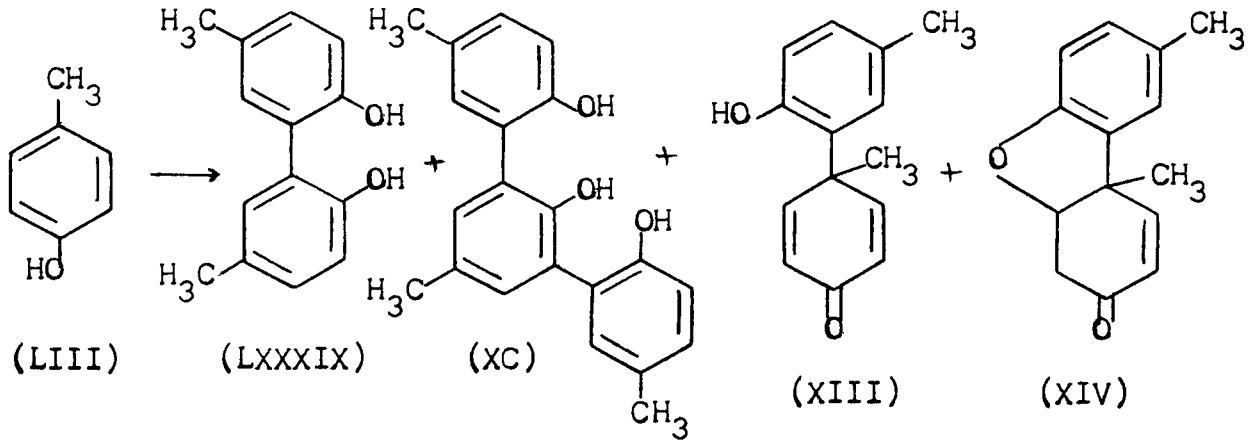
However, isodurene (LXXXV) on oxidation with manganese (III) acetate in the presence of sulphuric acid undergoes side chain oxidation and benzyl acetates LXXXVI, LXXXVII and LXXXVIII, accompanied by small amounts of carbonyl compounds, were obtained[33].



(LXXXV) (LXXXVI) (LXXXVII) (LXXXVIII)

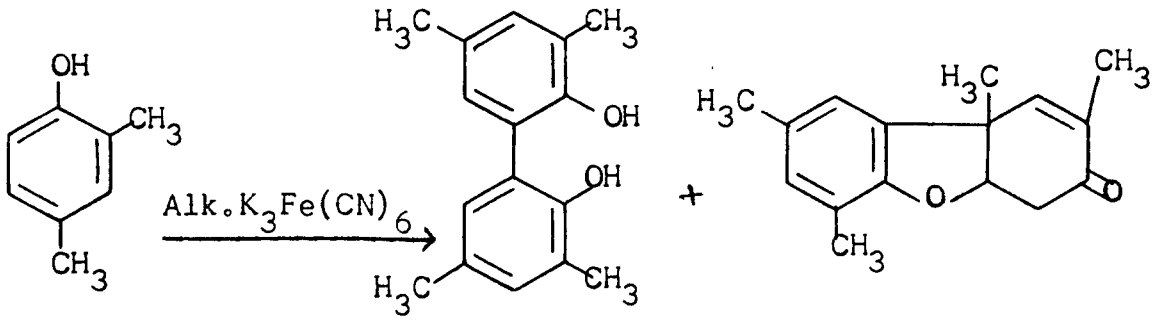
METAL ION OXIDATION OF PHENOLS

Oxidation of p-cresol (LIII) has been carried out by a large number of oxidizing agents. Oxidation with alkaline potassium ferricyanide yields compounds XIII, XIV, LXXXIX and XC. Ferric chloride oxidation of p-cresol gave Pummerer's ketone (XIV) and trimer (XC)[9], while only dimer (LXXXIX) was obtained by the oxidation with LTA in benzene[35]. Pummerer's ketone (XIV) was also formed when p-cresol was oxidized by iron complex $[Fe(DMF)_3Cl_2][FeCl_4]$[36].



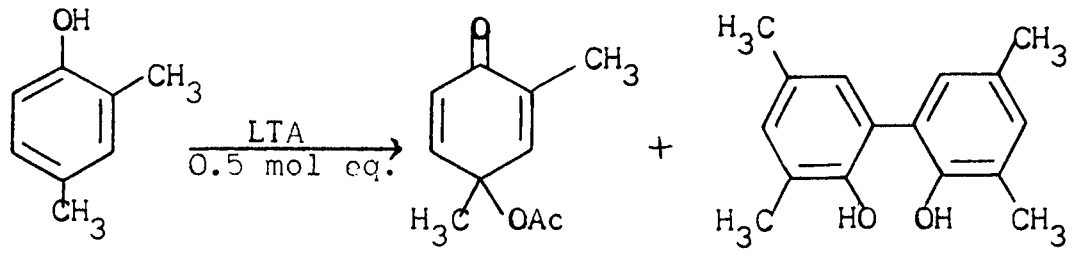
Oxidation of 2,4-xylenol (XCI) has been carried out with various reagents and in most cases o-o coupled diphenol is the major product. Alkaline potassium ferricyanide[8] oxidation of 2,4-xylenol gave 2,2'-dihydroxy-3,3',5,5'-tetramethylbiphenyl (XCII)

in 50% yield. Pummerer's ketone (XCIII) was also obtained as a minor product. Oxidation of 2,4-xylenol with Cu(II) toluate[37] and free hydroxyl radical[38] afforded good yields of biphenyl (XCII).

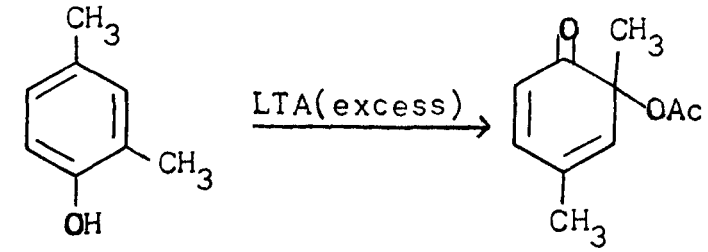


(XCI) (XCII) (XCIII)

In the oxidation of 2,4-xylenol with LTA[35], the formation of the products (XCII) and/or acetoxy cyclohexadienones (XCIV) and (XCV) vary with the solvents and proportion of the oxidizing agent. Thus, oxidation with 0.5 molar equivalent of LTA in benzene afforded dihydroxydiphenyl (XCII) alongwith minor amount of 4-acetoxycyclohexadienone (XCIV), while with excess of LTA in benzene no dihydroxydiphenyl was obtained and the only product isolated was 2-acetoxycyclohexadienone (XCV).

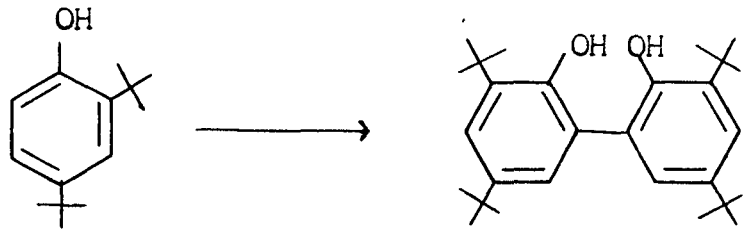


(XCI) (XCIV) (XCII)



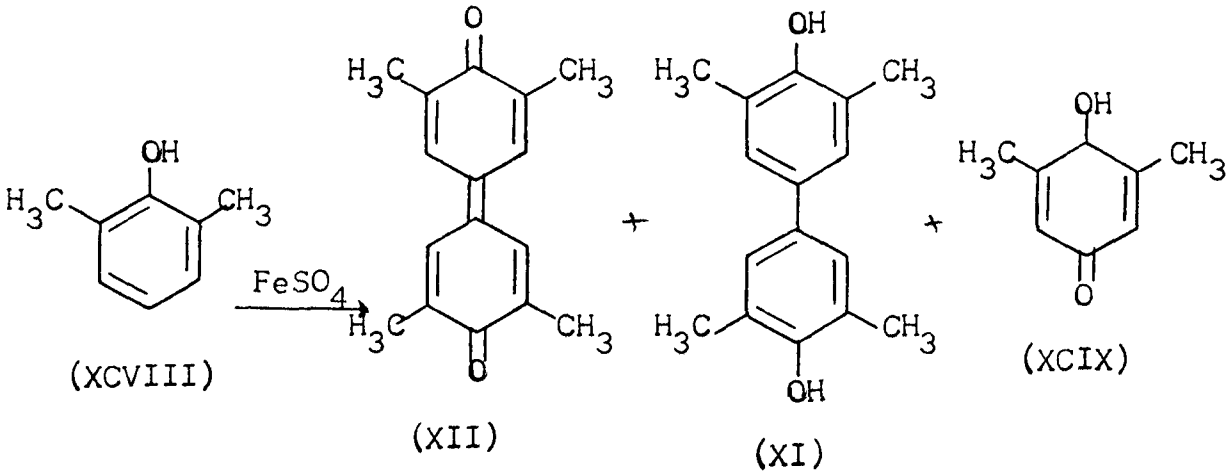
(XCI) (XCV)

Oxidation of 2,4-di-t-butylphenol (XCVI) with alkaline potassium ferricyanide[39] and Cu(II) toluate[37] has been reported to give 2,2'-dihydroxy-3,3',5,5'-tetra-t-butylbiphenyl (XCVII) in 81 and 57% yields, respectively.

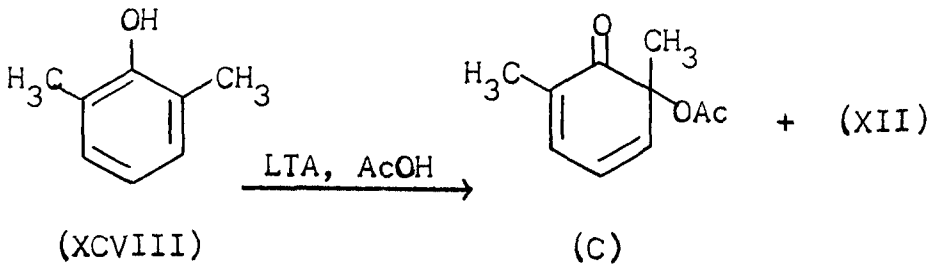


(XCVI) (XCVII)

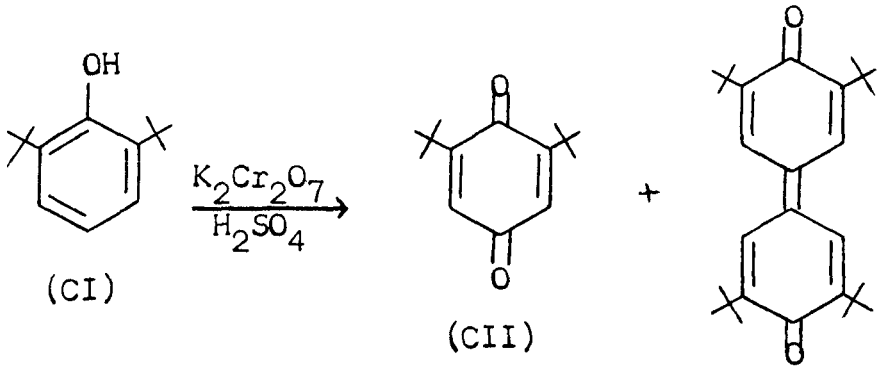
Oxidation of XCVIII with Cu(II) toluate[37] and ferrocene[40] affords good yield of 4,4'-dihydroxy-3,3',5,5'-tetramethylbiphenyl (XI) only, while ferrous sulphate[38] oxidation yields a mixture of diphenol (XI), diphenoquinone (XII) and 2,6-dimethyl-p-quinol (XCIX).



Compounds (XI) and (XII) have also been prepared by the lead tetra acetate oxidation of 2,6-xylenol in benzene[35], while in acetic acid, 2-acetoxy-2,6-dimethylcyclohexadienone (C) was also obtained besides diphenoquinone (XII).

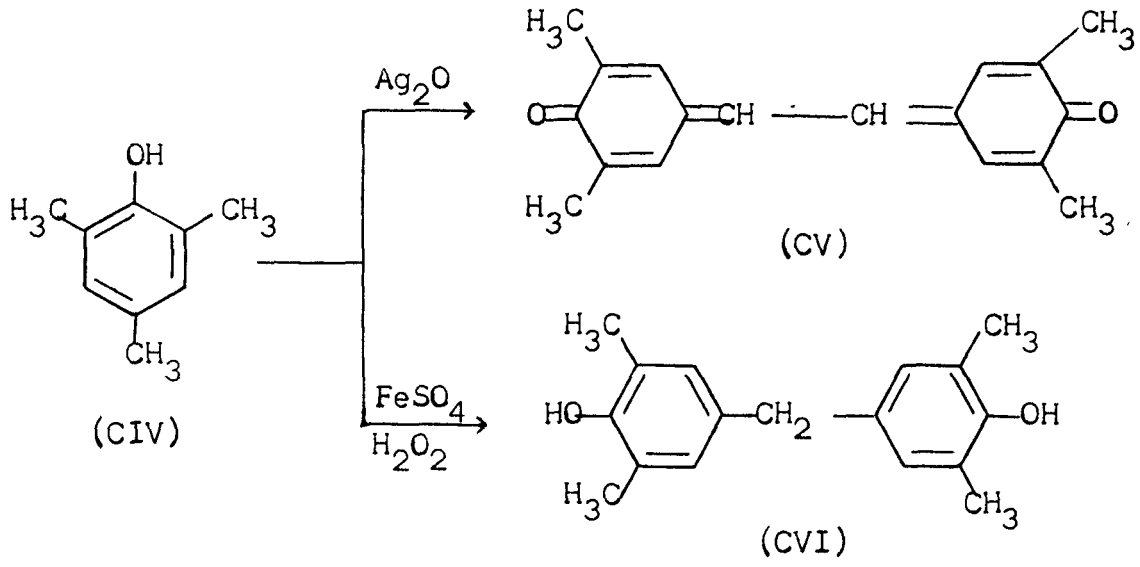


Benzoquinone (CII) was obtained as the major product alongwith minor amount of diphenoquinone (CIII) on oxidation of 2,6-di-t-butylphenol (CI) with potassium dichromate[41].



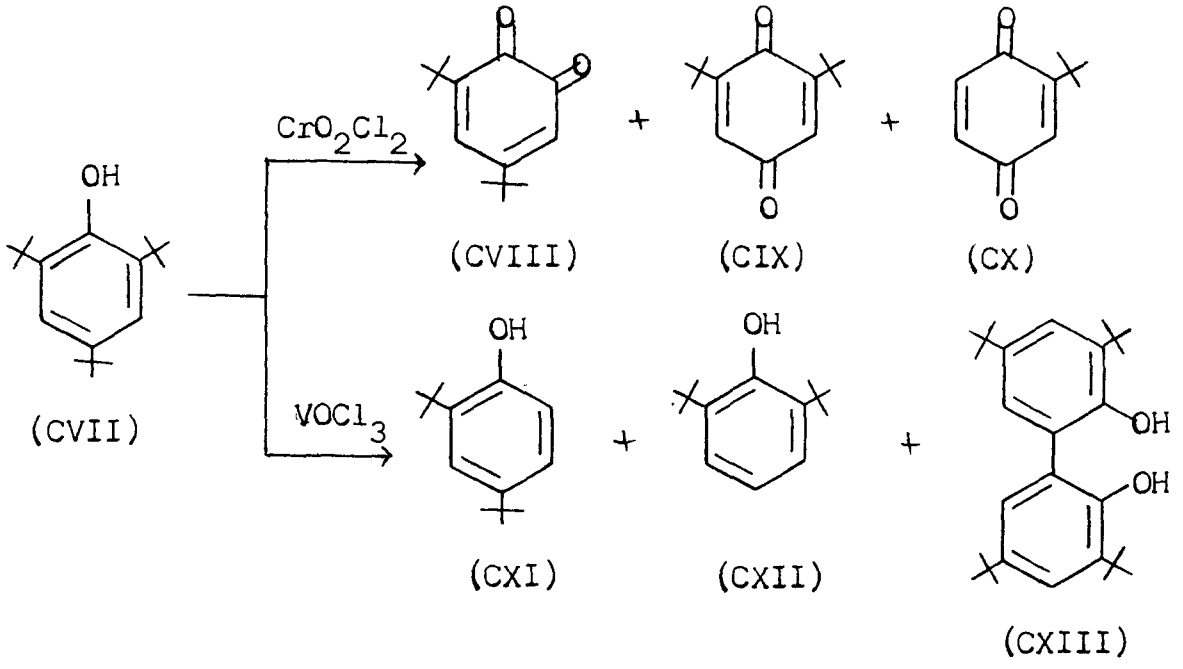
(CI) (CII) (CIII)

Oxidation of mesitol (CIV) has been studied with various reagents and products derived from benzyl radical have been isolated. Stilbenequinone (CV) was formed on oxidation of mesitol with silver(II) oxide[42], while diarylmethane (CVI) was obtained on oxidation with ferrous sulphate[38].

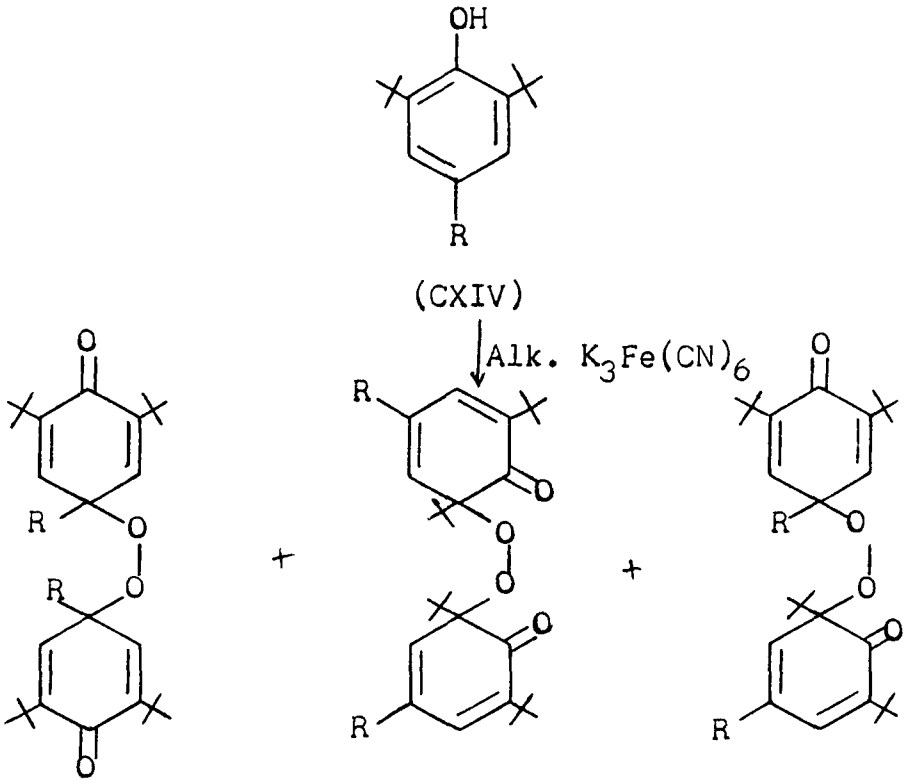


(CIV) (CV) (CVI)

Oxidation of 2,4,6-tri-t-butylphenol (CVII) by CrO_2Cl_2 and $VOCl_3$ has been studied[43]. The products of chromyl chloride oxidation are mostly quinones, CVIII-CX, while those of vanadyl chloride oxidation products include major dealkylated phenols, CXI, CXII and C-C coupled dimer (CXIII).

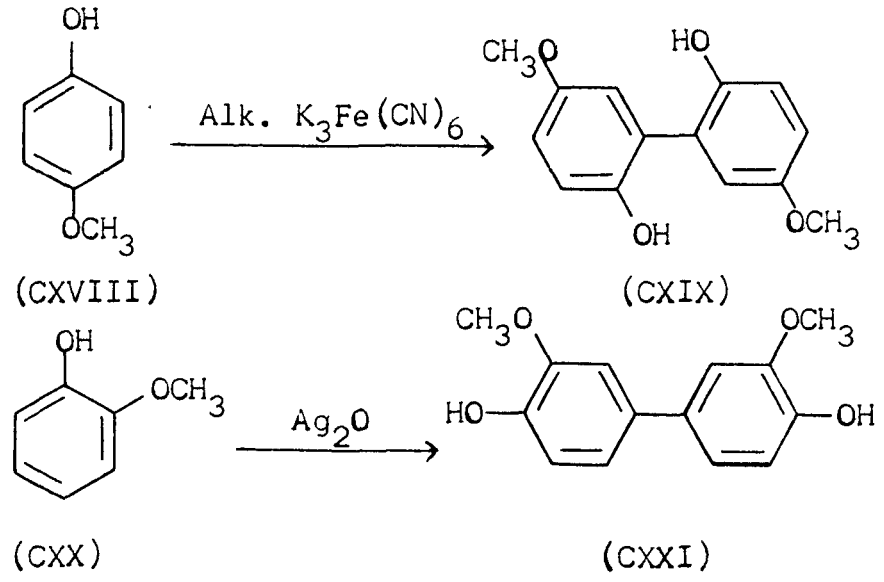


Batanov et al.[44] have carried out oxidation of 2,4,6-trisubstituted phenols (CXIV) [R= $-CMe_3$, $-CHMe_2$, -OMe, Ph-, -COPh] with alk. $K_3Fe(CN)_6$ and isolated compounds CXV, CXVI and CXVII in different ratios.



METAL-ION OXIDATION OF ALKOXY PHENOLS

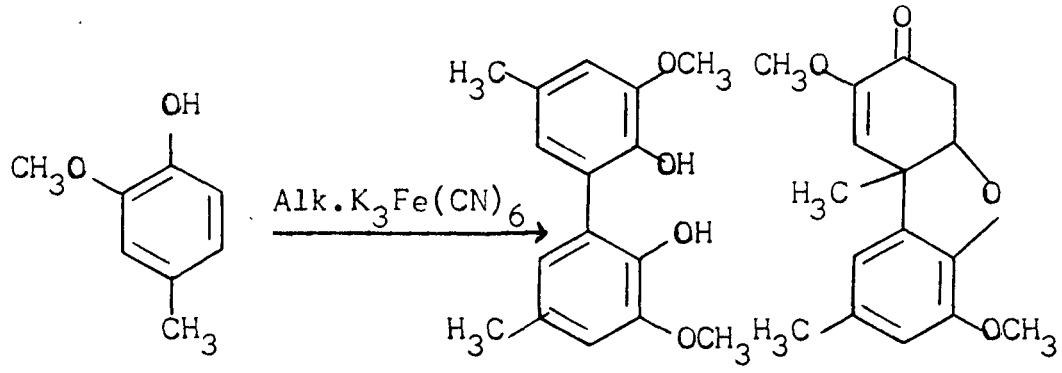
p-Methoxyphenol (CXVIII) on oxidation with potassium ferricyanide in the presence of sodium acetate afforded 2,2'-dihydroxy-5,5'-dimethoxybiphenyl (CXIX)[8]. Oxidation of o-methoxyphenol (CXX)[45] with $K_3Fe(CN)_6$ yielded polyether only. Silver(II) oxide oxidation of CXX gave 4,4'-dihydroxy-3,3'-dimethoxybiphenyl (CXXI) in only 1% yield and polyether.



(CXVIII) (CXIX)

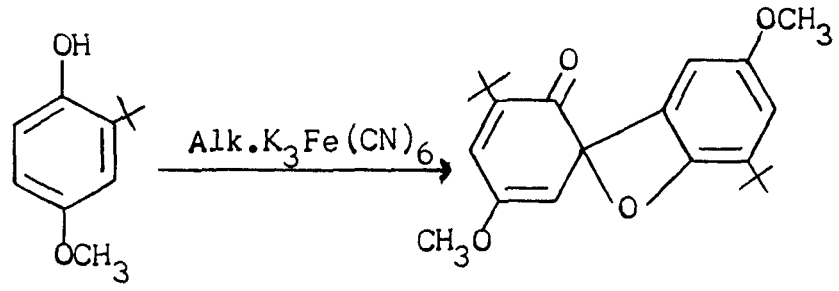
(CXX) (CXXI)

2,2'-Dihydroxy-3,3'-dimethoxy-5,5'-dimethylbiphenyl (CXXIII) was obtained in 60% yield by the ferricyanide oxidation of 2-methoxy-4-methylphenol (CXXII)[8]. Pummerer's ketone (CXXIV) was also formed as the minor product.



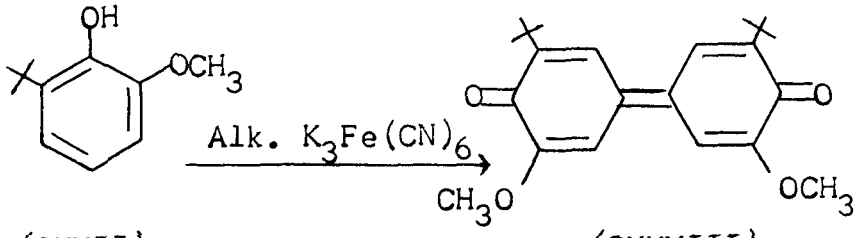
(CXXII) (CXXIII) (CXXIV)

Oxidation of 2-t-butyl-4-methoxyphenol (CXXV) with alkaline potassium ferricyanide in hexane yielded product CXXVI in 85% yield[46].



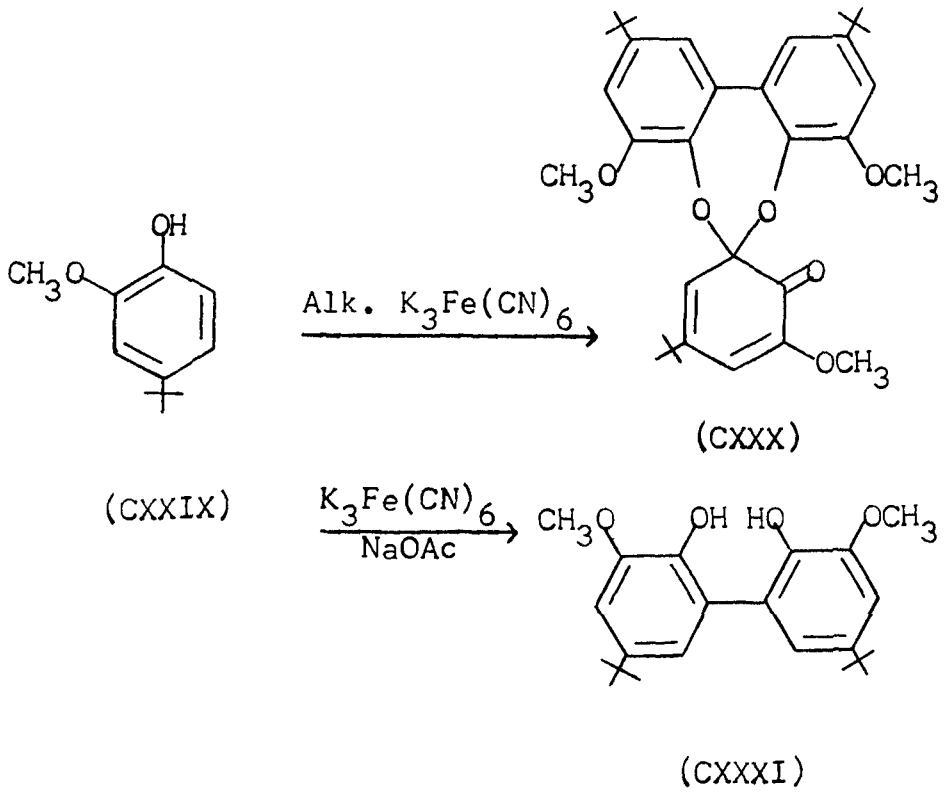
(CXXV) (CXXVI)

Diphenoquinone (CXXVIII) was obtained in good yield by the alkaline potassium ferricyanide oxidation 2-t-butyl-6-methoxyphenol (CXXVII)[47].

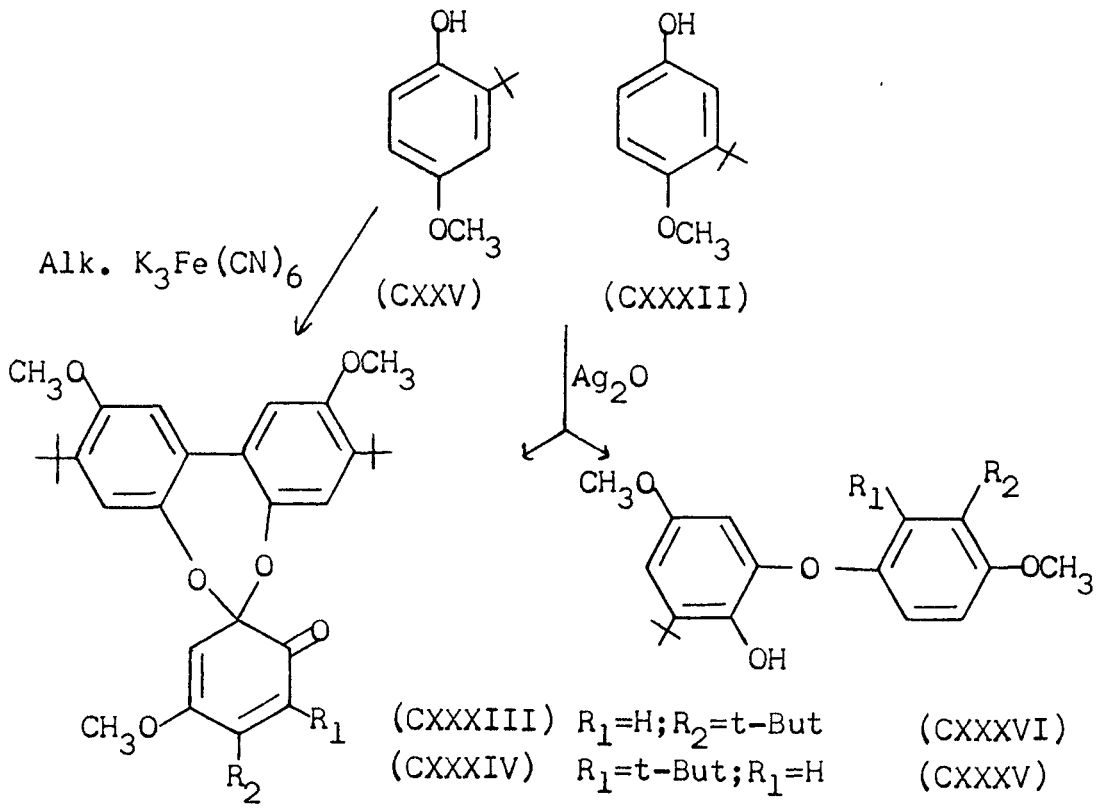


(CXVII) (CXXVIII)

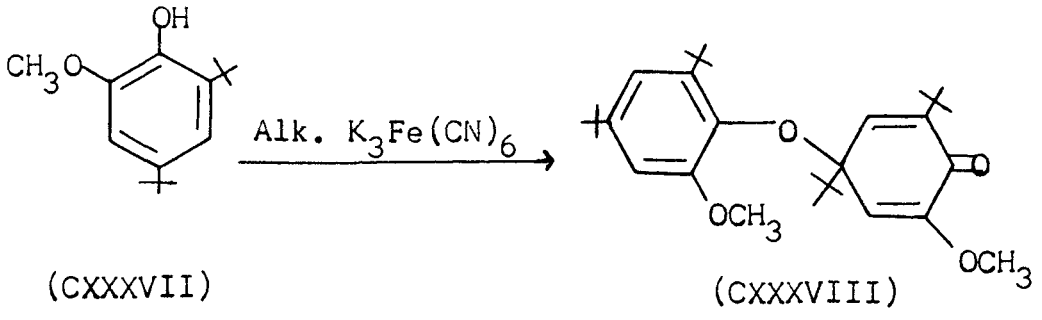
Hewgill and co-workers have studied the oxidation of alkoxy phenols in detail. They have found that alkaline potassium ferricyanide oxidation of 4-t-butyl-2-methoxyphenol (CXXIX) afforded a trimer (CXXX), while $K_3Fe(CN)_6$ in the presence of sodium acetate gave 2,2'-dihydroxy-3,3'-dimethoxy-5,5'-di-t-butylbiphenyl (CXXXI)[47].



They have also studied the oxidation of a mixture of phenols. Thus, oxidation of a mixture of 2-t-butyl-4-methoxy- and 3-t-butyl-4-methoxyphenols (CXXV) and (CXXXII) with alkaline $K_3Fe(CN)_6$[48] gave dio-xephins, CXXXIII and CXXXIV, while Ag_2O oxidation of the above mixture of phenols afforded hydroxydiphenyl ethers, CXXXV and CXXXVI, besides spiro-acetals, CXXXIII and CXXXIV . They have inferred from these results that CXXXVI is probably the intermediate in the formation of spiro-acetals.[49]

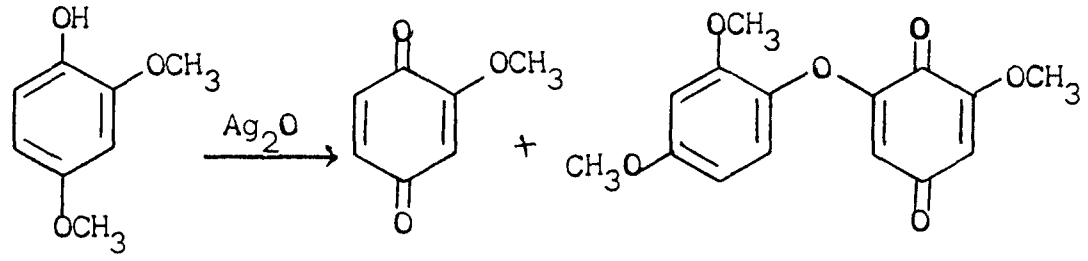


Oxidation with alkaline potassium ferricyanide of 2,4-di-t-butyl-6-methoxyphenol (CXXXVII) gave p-quinolether (CXXXVIII)[50].



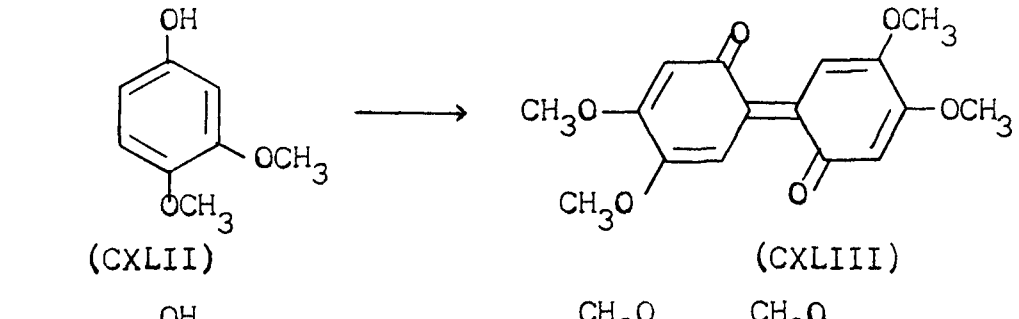
(CXXXVII) (CXXXVIII)

Oxidation of 2,4-dimethoxyphenol (CXXXIX) with silver(II) oxide resulted in the formation of methoxy-1,4-benzoquinone (CXL) and 2-(2,4-dimethoxyphenoxy)-6-methoxy-1,4-benzoquinone (CXLI)[51].

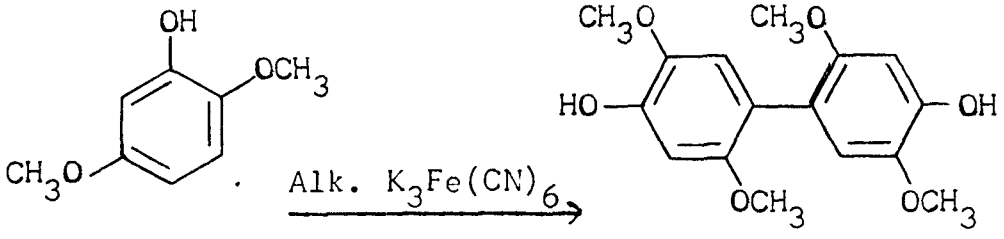


(CXXXIX) (CXL) (CXLI)

3,4-Dimethoxyphenol (CXLII) afforded 4,4',5,5'-tetramethoxydipheno-2,2'-quinone (CXLIII) on oxidation with alkaline potassium ferricyanide, while 2,5-dimethoxyphenol (CXLIV) afforded, on oxidation with alkaline ferricyanide 4,4'-dihydroxy-2,2',5,5'-tetramethoxybiphenyl (CXLV)[51].

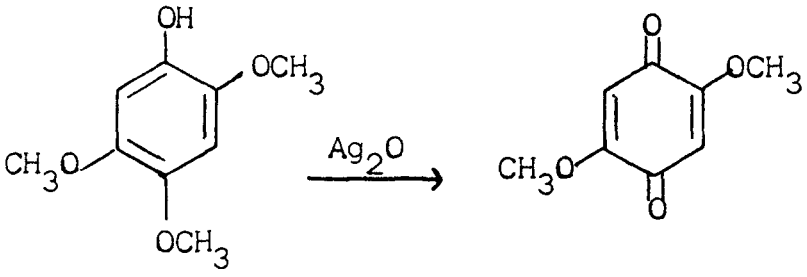


(CXLII) (CXLIII)



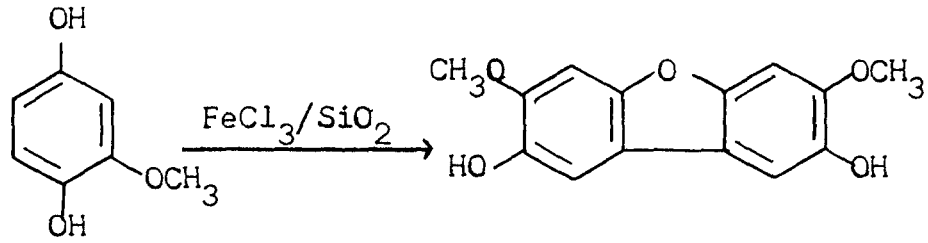
(CXLIV) (CXLV)

2,4,5-Trimethoxyphenol (CXLVI) undergo demethylation during oxidation with silver(II) oxide and give 2,5-dimethoxy-1,4-benzoquinone (CXLVII)[51].



(CXLVI) (CXLVII)

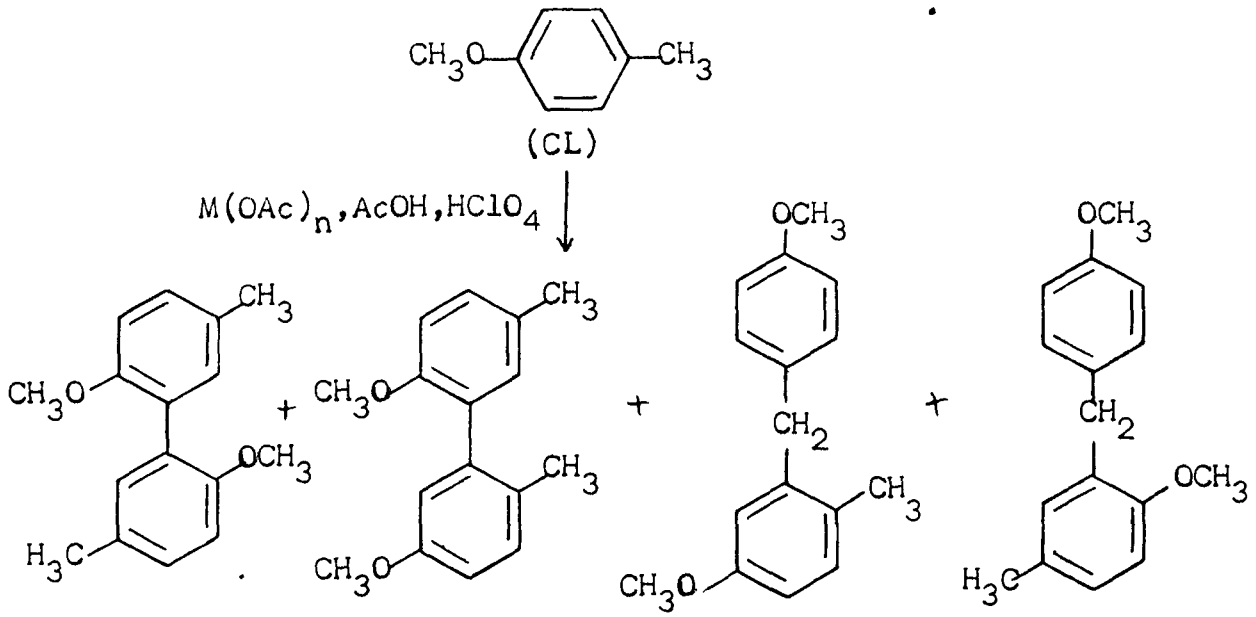
Silica bound ferric chloride has also been found as a good oxidant for oxidation of methoxyphenols. Thus, oxidation of 4-hydroxy-2-methoxyphenol (CXLVIII) with silica bound ferric chloride afforded CXLIX[52].



(CXLVIII) (CXLIX)

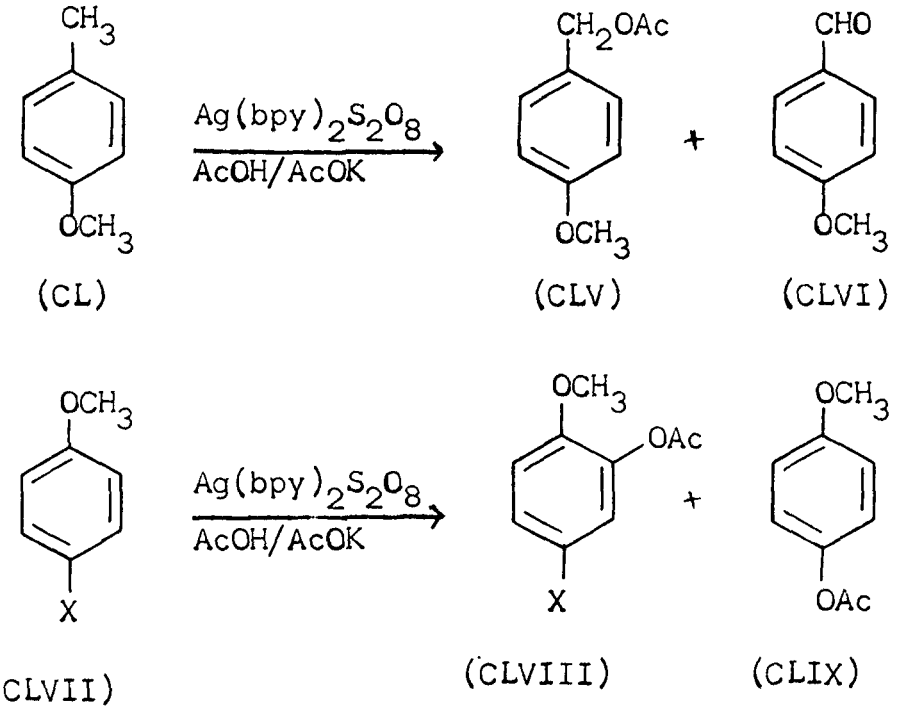
METAL-ION OXIDATION OF ALKOXY BENZENES

p-Methoxytoluene (CL)[53] afforded biphenyls, CLI and CLII as the main products, when oxidized by Mn(III) acetate in acetic acid containing strong acid ($HClO_4$, CF_3SO_3H or H_2SO_4). In the presence of less strong acids such as CF_3COOH or CCl_3COOH or a low concentration of perchloric acid, however, diarylmethane (CLIII and CLIV) were main products. On the other hand, in the oxidation reaction with Fe(III) acetate, diarylmethanes, CLIII and CLIV were the only products even in the presence of strong acids. The different behaviour of the metal acetates was explained by assuming a considerable difference in the stability of an oxygen centred trinuclear species which work as a base to remove proton from a radical cation intermediate.



(CLI) (CLII) (CLIII) (CLIV)

Nyberg[28] and co-workers have studied the oxidation of some aromatic compounds with some Ag(II) complexes in acetic acid. Side chain acetoxylation occurs in the case of p-methoxytoluene, (CL), while nuclear acetoxylated products have been obtained in the reaction of CLVII with Ag(II) complexes.

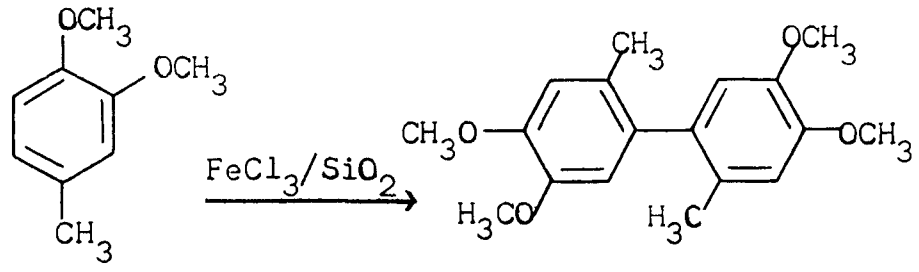


(CL) (CLV) (CLVI)

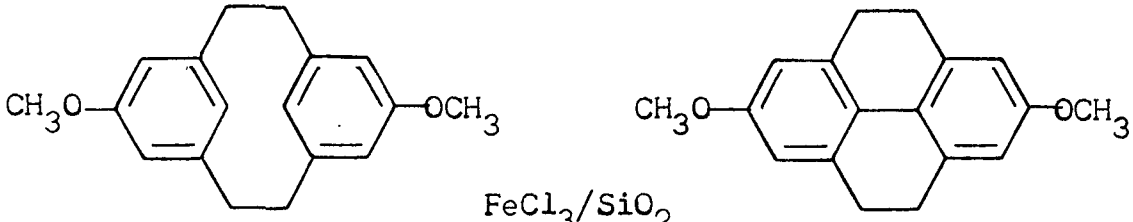
(CLVII) (CLVIII) (CLIX)

X= F, Cl, t-But

Jempty et al.[52] have investigated the oxidation of some aromatic substrates with silica bound $FeCl_3$. Thus, silica bound ferric chloride oxidation of CLX and CLXI afforded C-C coupled products, CLXII and CLXIII, respectively.



(CLX) (CLXII)



(CLXI) (CLXIII)

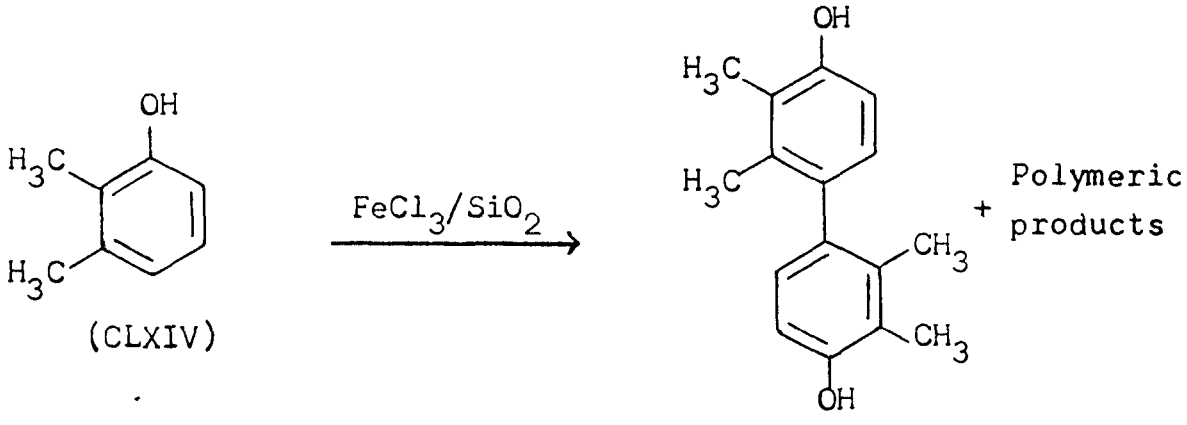
DISCUSSION

It has been suggested that the carcinogen induced cancer can be prevented by free radical scavangers[54]. The hindered phenols, the free radicals of which are stable because steric hinderance prevents their dimerization[55], make good anticancer agents[56]. Thus, phenols which can act as anticancer agents even after dimerization as their free radicals will be more stable may prove more useful. This prompted us to study the oxidation of phenolic compounds for the synthesis of dimeric phenolic derivatives.

Though, the oxidation of phenols with an unsubstituted ortho or para position has extensively been explored, little attention has been paid to the phenols with an ortho and para unsubstituted positions. While 2,4- and 2,6-disubstituted phenols give, on oxidation, dimeric phenols with all the ortho and para positions blocked by substituents, the dimeric products of 2,3-disubstituted phenols will still have a free ortho or para position. 2,3-Dimethylphenol was, therefore, chosen as a model substrate and its reactions with silica bound ferric chloride[52], $[Fe(DMF)_3Cl_2][FeCl_4]$[36] and copper(II) acetate-perchloric acid-acetic acid reagent system[53] have been studied. Our choice of oxidants was prompted by the fact that Fe(III) and Cu(II) ions are frequently encountered in nature[57,58].

Reaction of 2,3-dimethylphenol with silica bound ferric chloride

The reaction of 2,3-dimethylphenol with silica bound ferric chloride was carried out in the following manner. A solution of 2,3-dimethylphenol (CLXIV) in dichloromethane was added to ferric chloride (molar ratio of substrate and ferric chloride was 1:2) adsorbed on appropriate amount of silica gel. The solvent was evaporated and the reaction mixture was left rotating on a rotary evaporator for 2 hours. Ether and water were then added. The reaction mixture was stirred and filtered. The organic layer was washed, dried and evaporated to give a crude brown solid which was chromatographed on a silica gel column. After the recovery of the unreacted starting material, a white crystalline product was obtained which was characterized by spectral methods as 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV). Further elution of the column yielded a complex mixture of polymeric products which could not be purified even on repeated column chromatography.



(CLXIV)

(CLXV)

Characterization of 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV)

The compound melting at 192-4°C showed, in its mass spectrum (Fig. 1), the molecular ion peak at m/z 242 suggesting it to be a dehydrodimer of 2,3-dimethylphenol. It gave positive alcoholic ferric chloride test. The presence of hydroxy group was further confirmed by its i.r. spectrum (Fig. 2) which displayed band at 3320 cm^{-1}. The aromatic stretching bands at 2940, 1580 and 1440 cm^{-1} were also present. The structure of this compound was further elucidated with the help of ^{1}H-n.m.r. and mass spectra. Mass spectrum exhibited only a few prominent peaks suggesting thereby that the molecule is highly stable. Molecular ion peak observed at m/z 242, was the base peak. Other prominent peaks were at m/z 227 ($M-CH_3$) and at m/z 212 ($M-2xCH_3$). A small peak at m/z 197 may be attributed to the loss of three methyl groups from the molecular ion. Some less intense peaks at m/z 121 and 106 may be due to the doubly charged ions M^{++} and $(M-2xCH_3)^{++}$, respectively.

^{1}H-n.m.r. spectrum (Fig. 3) clearly indicated the symmetrical nature of the product. It displayed two singlets at δ 1.95 and 2.22, each for six protons, which were assigned to the protons of the four methyl groups. A singlet at δ 4.64 for two protons which disappeared on shaking with D_2O was attributed to two phenolic protons. Two ortho coupled doublets (J=9 Hz), each for two protons,

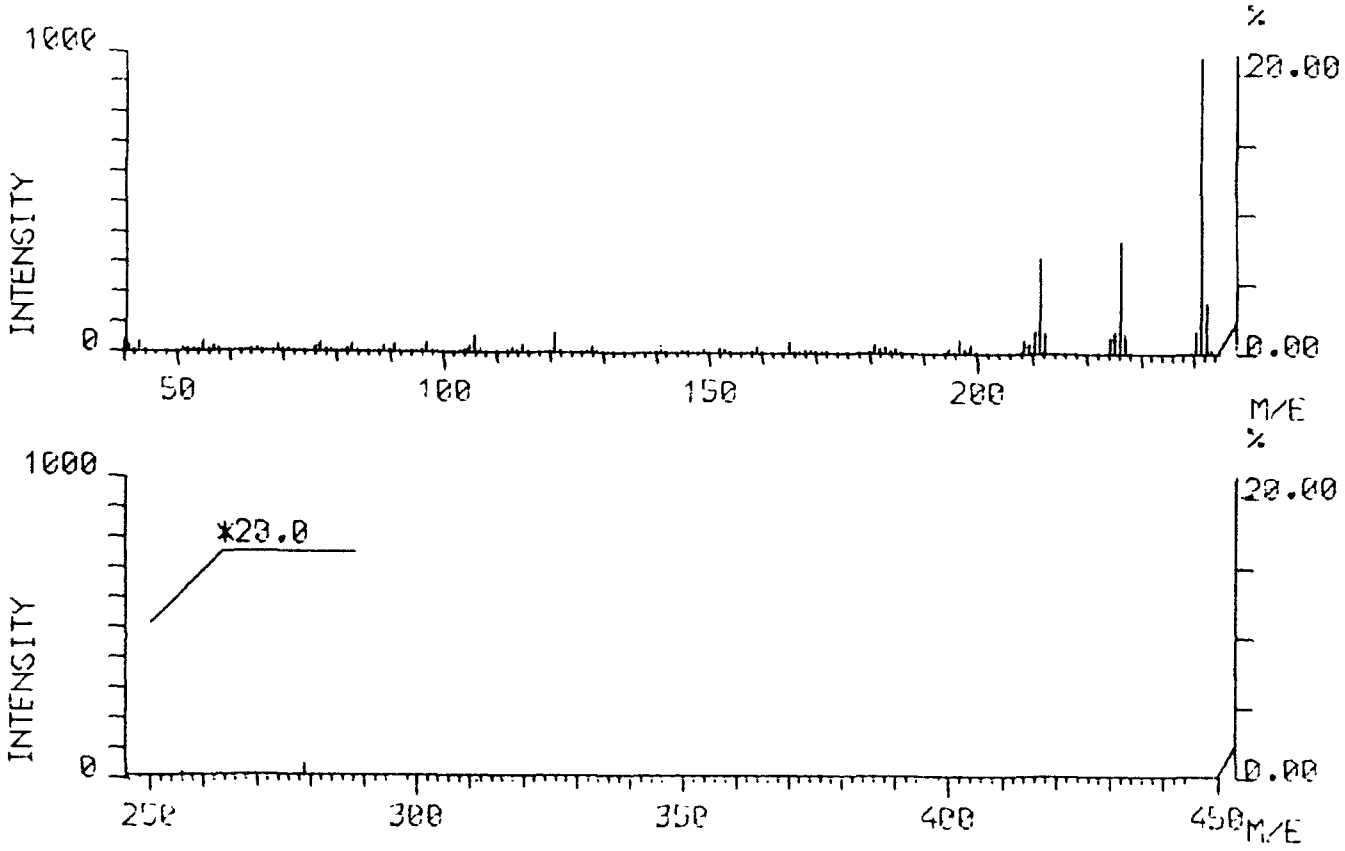

1000
INTENSITY
0
50
100
150
200
%
20.00
0.00
M/E
1000
INTENSITY
0
*23.0
250
300
350
400
450
M/E
%
20.00
0.00

Fig. 1

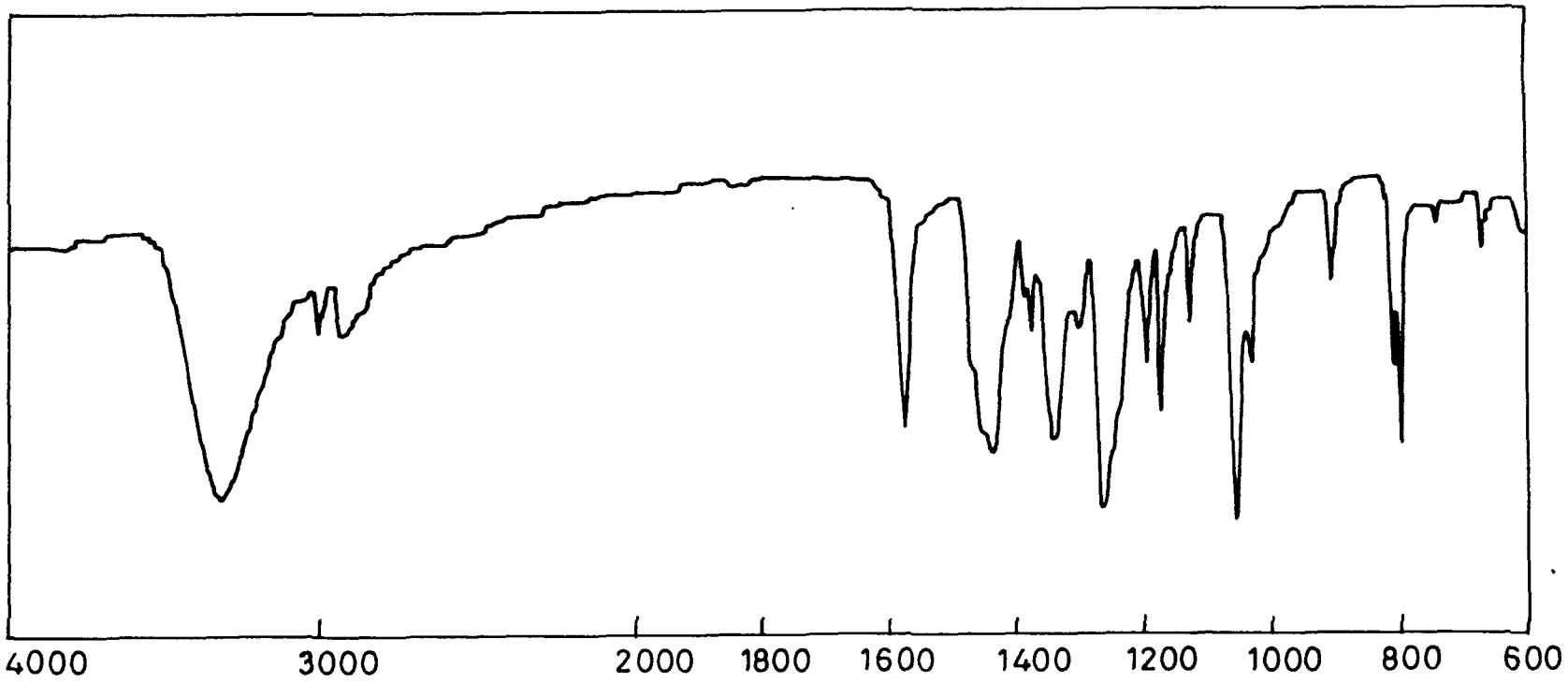


FIG. 2

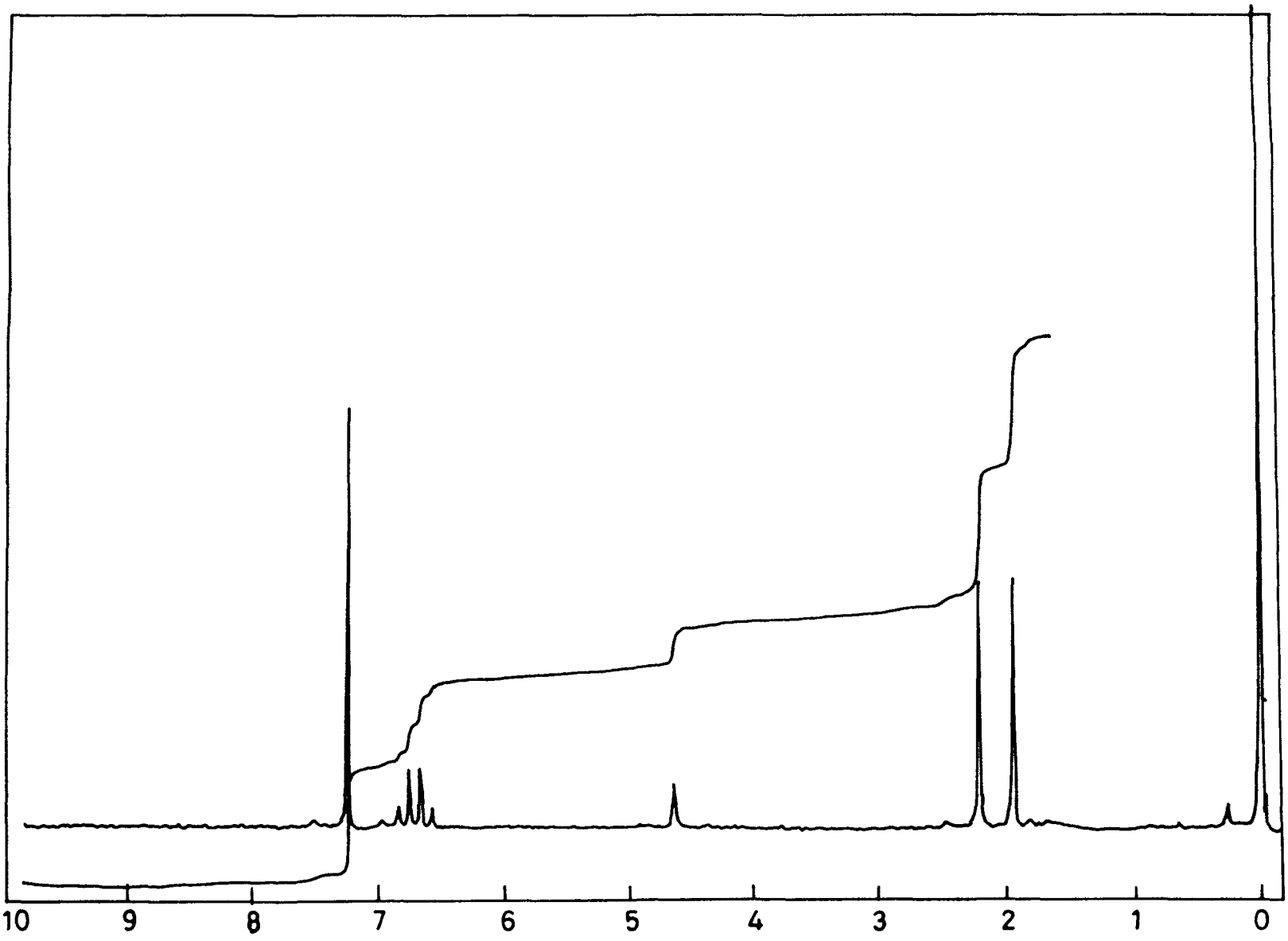


FIG. 3

at ∂ 6.63 and 6.81 were imputed to four aromatic protons. Of the two possible assignments, the compound was characterized as 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) as it gave negative Gibb's test[59]. Chemical shift data of compound (CLXV) is shown in table I.

Table I

Chemical shifts of protons of 4,4'-dihydroxy-2,2',3,3'-tetramethyl-biphenyl (CLXV).

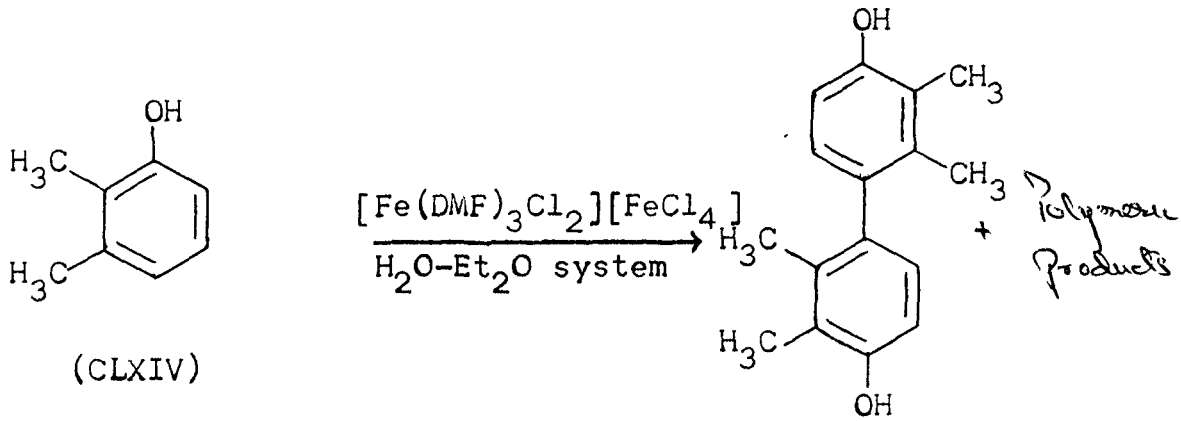
Proton Assignment	Chemical shifts (∂ ppm)
CH_3-2,2'	1.95 (s, 6H)
CH_3-3,3'	2.22 (s, 6H)
HO-4,4'	4.64 (s, 2H)
H-6,6'	6.63 (d, J=9 Hz, 2H)
H-5,5'	6.81 (d, J=9 Hz, 2H)

s= singlet; d= doublet; spectrum run in $CDCl_3$ at 90 MHz; TMS as internal standard ∂= 0.00 ppm.

The amount of the polymeric products obtained in this reaction was far more than the diphenol, though the recovery of the starting material was excellent. It was, therefore, thought that the use of less than the required amount of ferric chloride may help in checking the polymerization. The reaction of 2,3-dimethylphenol with silica bound ferric chloride was, therefore, studied taking the substrate and the ferric chloride in the molar ratio of 5:1. The reaction was performed in the previously described manner. The reaction on usual work up and chromatographic purification yielded, besides unchanged 2,3-dimethylphenol and polymeric products, a white compound which was found identical to an authentic sample of 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) in all respects (m.m.p., i.r., ^{1}H-n.m.r. and mass spectral data). The ratio of the dimeric and polymeric products was, however, found almost unaffected and it is not yet fully understood why the oxidation of a monohydric phenol produces far more polymeric than the dimeric products[4c].

Reaction of 2,3-dimethylphenol with $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in heterogeneous medium

The reaction was carried out in two phases system in the following manner. 2,3-Dimethylphenol (CLXIV) (40.92 mmol) was dissolved in ether and the resulting solution added to an aqueous solution of $[Fe(DMF)_3Cl_2][FeCl_4]$ complex (81.8 mmol). The resulting mixture was then stirred at room temperature for eight hours. Aqueous layer was then removed and ethereal layer washed with water, dried and evaporated to give a crude product. Chromatographic purification of the crude mass furnished, besides unreacted starting material and polymeric products, a white solid which was identified as 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) by spectral methods.



(CLXIV)

(CLXV)

The i.r. and mass spectra of this product were almost identical to that of an authentic sample. However, the ^{1}H-n.m.r. spectrum was obtained in DMSO-d_6 and was somewhat different from that obtained in $CDCl_3$. ^{1}H-n.m.r. spectrum (Fig. 4) exhibited two singlets at ∂ 1.80 and 2.03, each for six protons, which were due to the four methyl groups. Another singlet at ∂ 8.62 for two protons was attributed to the two phenolic protons. The protons on the two aromatic rings did not appear as AB doublets but were seen as a singlet at ∂ 6.57 integrating for four protons. Chemical shift data of compound (CLXV) is given in table II.

Table II

Chemical shifts of protons of 4,4'-dihydroxy-2,2',3,3'-tetramethyl-biphenyl (CLXV).

Proton assignment	Chemical shifts (∂ ppm)
CH_3-2,2'	1.80 (s, 6H)
CH_3-3,3'	2.03 (s, 6H)
H-5,5',6,6'	6.57 (s, 4H)
HO-4,4'	8.62 (s, 2H)

s= singlet; spectrum run in DMSO-d_6 at 60 MHz; TMS as internal standard ∂= 0.00 ppm.

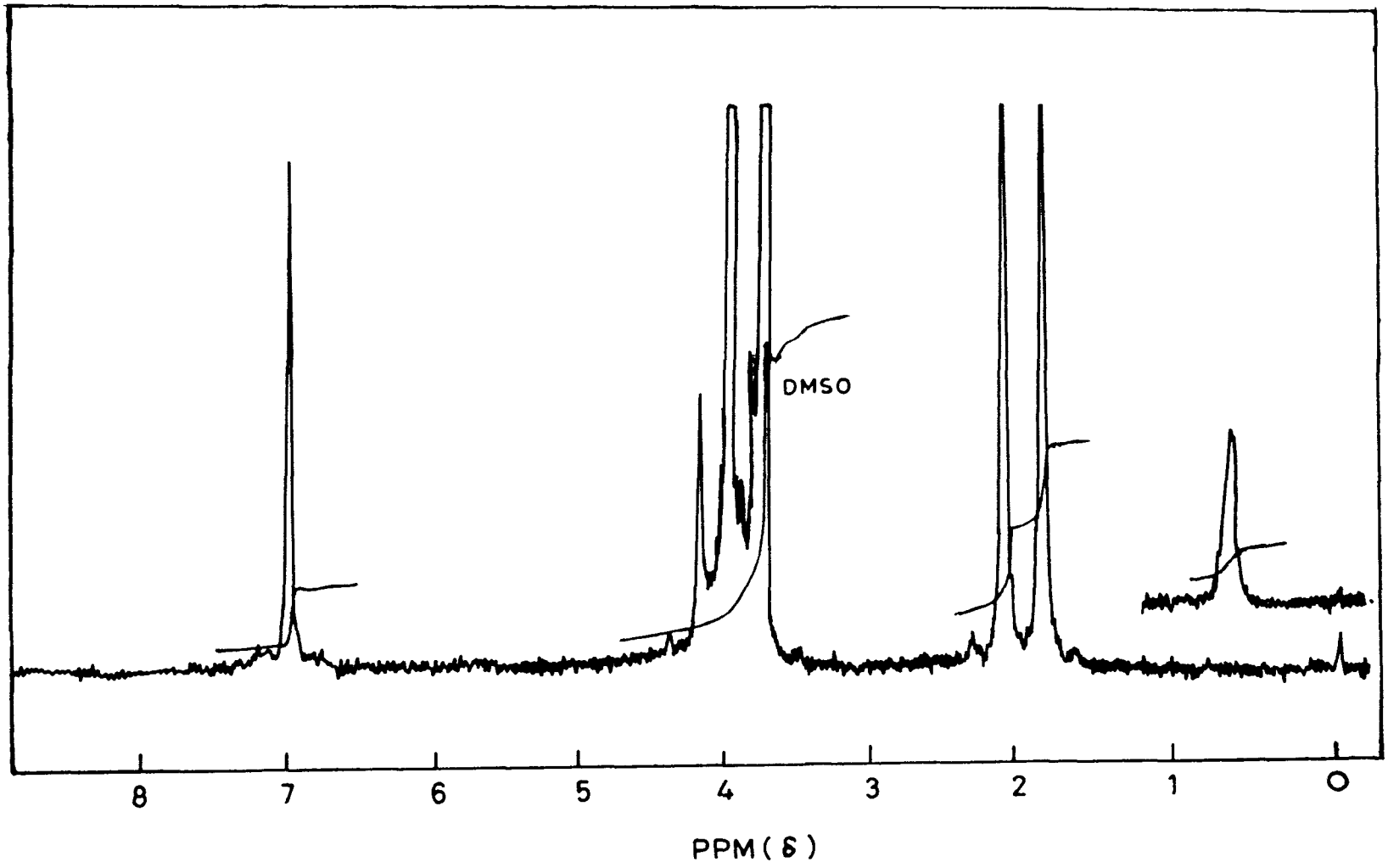
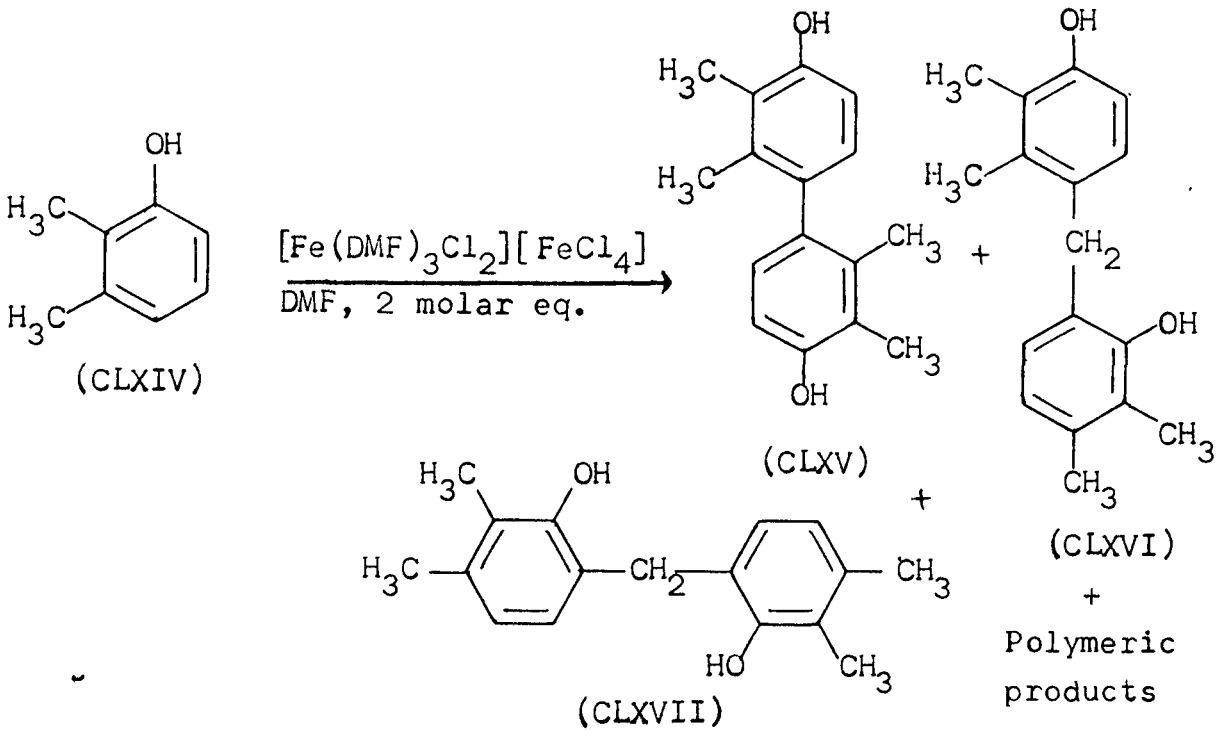


FIG. 4

Reaction of 2,3-dimethylphenol with $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in homogeneous medium in the molar ratio 1:2

The reaction was performed in the following manner. To a solution of $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in N,N-dimethylformamide was added 2,3-dimethylphenol. The resulting mixture was heated at reflux temperature for ten hours. Water was then added and the organic material extracted with ether. Organic layer was washed, dried and evaporated to give a crude mass which was subjected to column chromatography over a silica gel column. Unreacted 2,3-dimethylphenol was eluted with petrol. Further elution of the column with different solvent systems furnished three products. Of the three, the major product was found identical to an authentic sample of 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) in all respects (m.m.p., i.r., n.m.r. and mass spectral data). Remaining two products were characterized by spectral methods as 4-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVI) and 6-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVII). A mixture of polymeric products was obtained when the column was eluted with benzene:ethyl acetate (1:1).



Characterization of 4-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVI)

The product melting at 119-21°C showed molecular ion peak at m/z 256 in its mass spectrum (Fig. 5). It gave positive alcoholic $FeCl_3$ test. The presence of hydroxy group was confirmed by the absorption band at 3340 cm^{-1} in the i.r. spectrum (Fig. 6). The structure was further elucidated with the help of ^1H-n.m.r. and mass spectra. The mass spectrum exhibited molecular ion peak at m/z 256 accompanied by an $(M+H)^+$ peak at m/z 257. Fission of the diarylmethane linkage resulted in the formation of two structurally diagnostic fragments at m/z 122 and 135. The spectrum

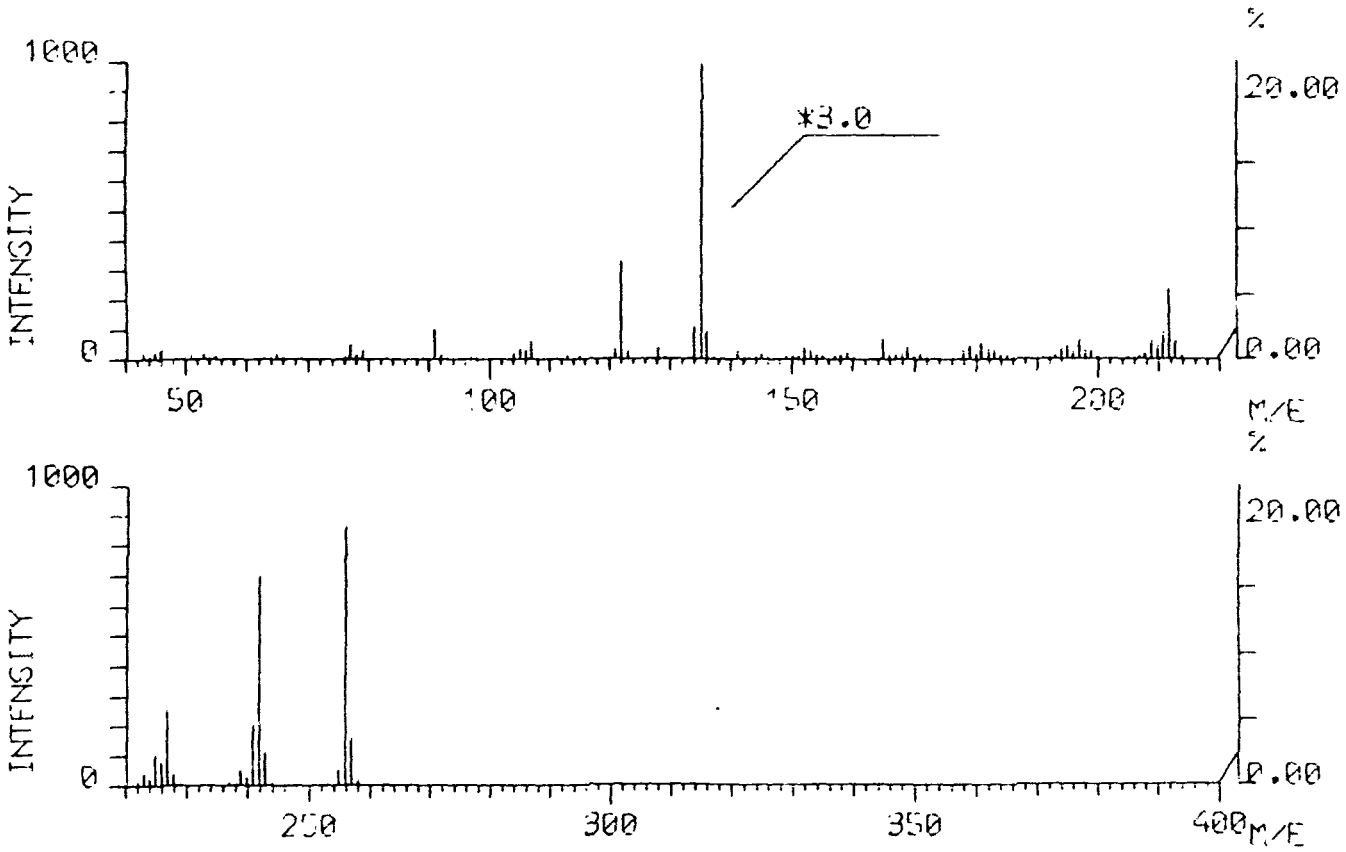

1000
INTENSITY
0
*3.0
%
20.00
0.00
50
100
150
200
M/E
%
1000
INTENSITY
0
20.00
0.00
250
300
350
400
M/E

Fig. 5

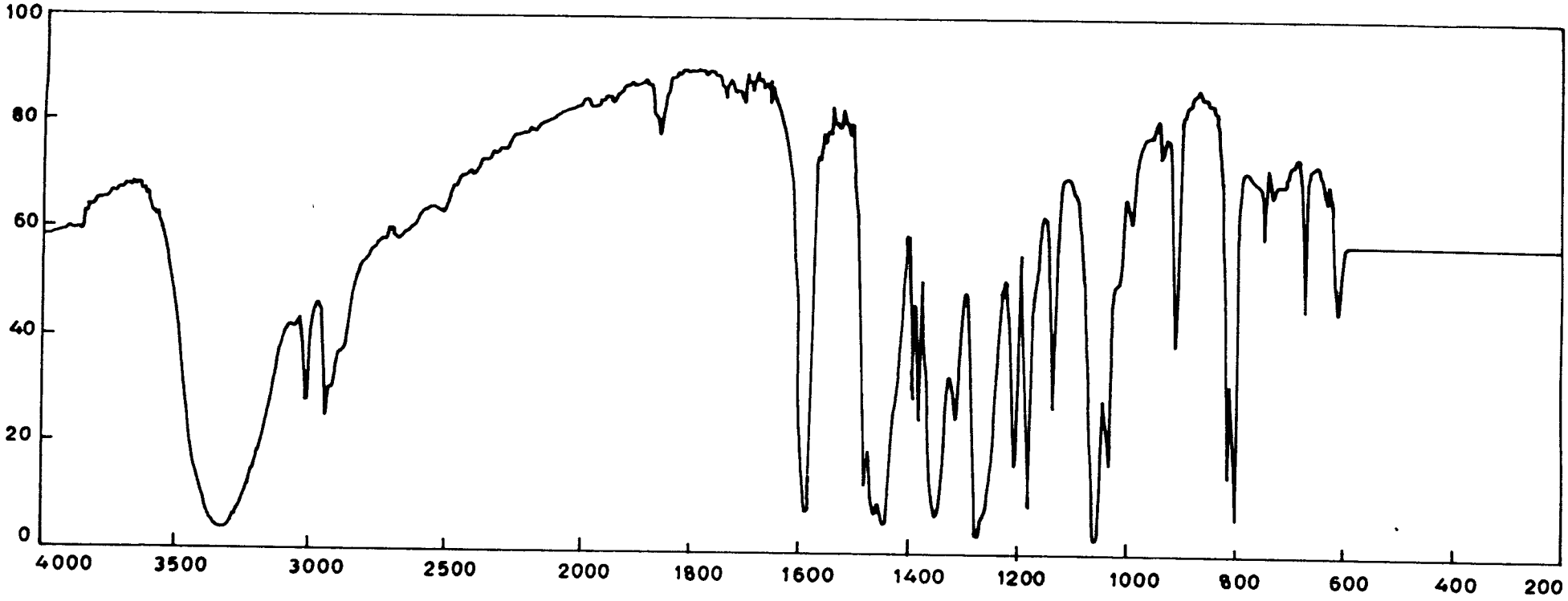
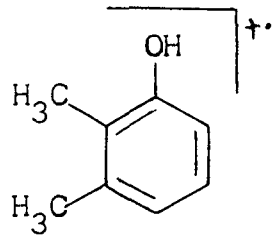
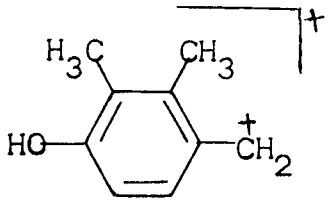


FIG. 6

did not show any other prominent peak except at m/z 242 which may be due to the ion formed by the loss of a methyl group from $M^{+\cdot}$ followed by a hydrogen abstraction. Some less intense peaks at m/z 227 and 212 may be attributed to the subsequent loss of methyl groups from the ion at m/z 242.



m/z 122



m/z 135

In the n.m.r. spectrum (Fig. 7), signals for the methyl protons were observed as singlets at ∂ 2.14, 2.18 and 2.24 integrating for three, six and three protons, respectively. A singlet at ∂ 3.87 for two protons was attributed to the methylene protons. Two more singlets at ∂ 4.54 and 4.68, each for one proton and exchangeable with D_2O, were assigned to the two phenolic protons. Aromatic region of the spectrum displayed a pair of doublets and a singlet. The pair of doublets (J=9 Hz) at ∂ 6.56 and 6.81, each for one proton and showing AB pattern, was imputed to the two ortho coupled protons on the C-5 and C-6, while the singlet at ∂ 6.68 for two protons was ascribed to the protons on other aromatic ring. The product was characterized as 4-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVI).

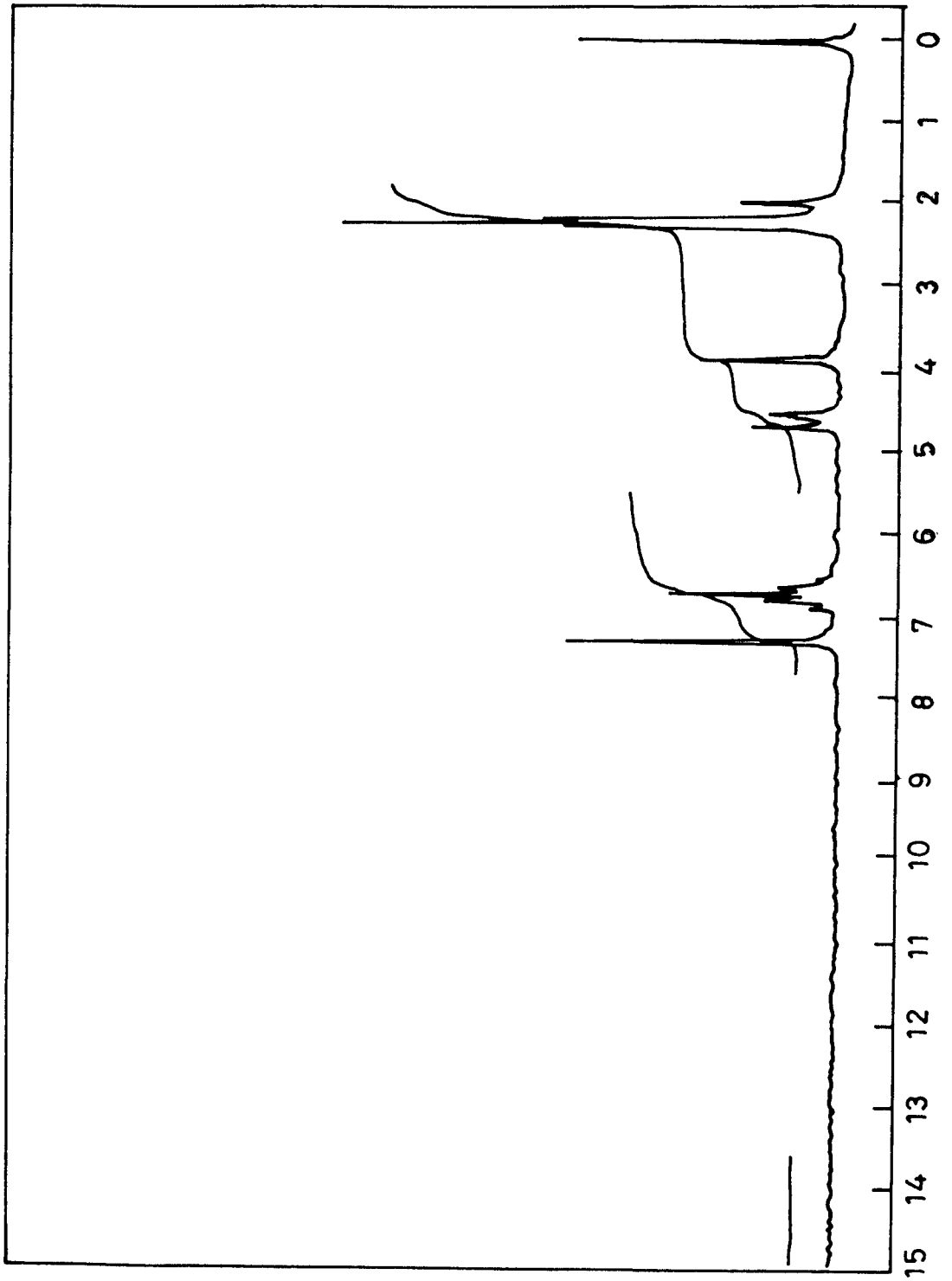


FIG. 7

The possibility of two other symmetrical assignments was ruled out in view of the unsymmetrical nature of the ^{1}H-n.m.r. spectrum. The chemical shift data of compound (CLXVI) is given in table III.

Table III

Chemical shifts of protons of 4-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVI).

Proton assignment	Chemical shifts (δ ppm)
CH_3-3'	2.14 (s, 3H)
CH_3-2,4'	2.18 (s, 6H)
CH_3-3	2.24 (s, 3H)
-CH_2-	3.87 (s, 2H)
HO-2'	4.54 (s, 1H)
HO-1	4.68 (s, 1H)
H-6	6.56 (d, J=9 Hz, 1H)
H-5',6'	6.68 (s, 2H)
H-5	6.81 (d, J=9 Hz, 1H)

s= singlet, d= doublet; spectrum run in $CDCl_3$ at 80 MHz;
TMS as internal standard δ= 0.00 ppm.

Characterization of 6-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVII)

The compound melting at 194-5°C exhibited, in the mass spectrum (Fig. 8), the $M^{+\cdot}$ peak at m/z 256. I.r. spectrum (Fig. 9) showed hydroxyl stretching band at 3250 cm^{-1}. Aromatic stretching bandswere seen at 3000, 1580 and 1480 cm^{-1}. The mass spectrum contained only a few prominent peaks. The most structurally diagnostic peak in the spectrum was at m/z 135 (100%) due to the ion formed by the fission of diarylmethane linkage. Other fragment resulting from this fission was seen at m/z 122. Few less intense peaks at m/z 241 $(M-CH_3)^+$, 107 $(m/z\ 122-CH_3)^+$ and 91 $(m/z\ 121-2xCH_3)^+$ were also present. N.m.r. spectrum (Fig. 10) revealed high symmetry in the molecule. Methyl protons were seen as two singlets at δ 2.15 and 2.20, each for six protons. Signal for the methylene protons was observed as a singlet at δ 3.81. A singlet at δ 6.54 for four protons was attributed to four aromatic protons. Another singlet at δ 7.35 for two protons was ascribed to two phenolic protons. Of the two possible assignments, o-o and p-p, the compound was characterized as 6-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVII) as it gave positive Gibb's test. The chemical shift data of compound (CLXVII) is given in table IV.

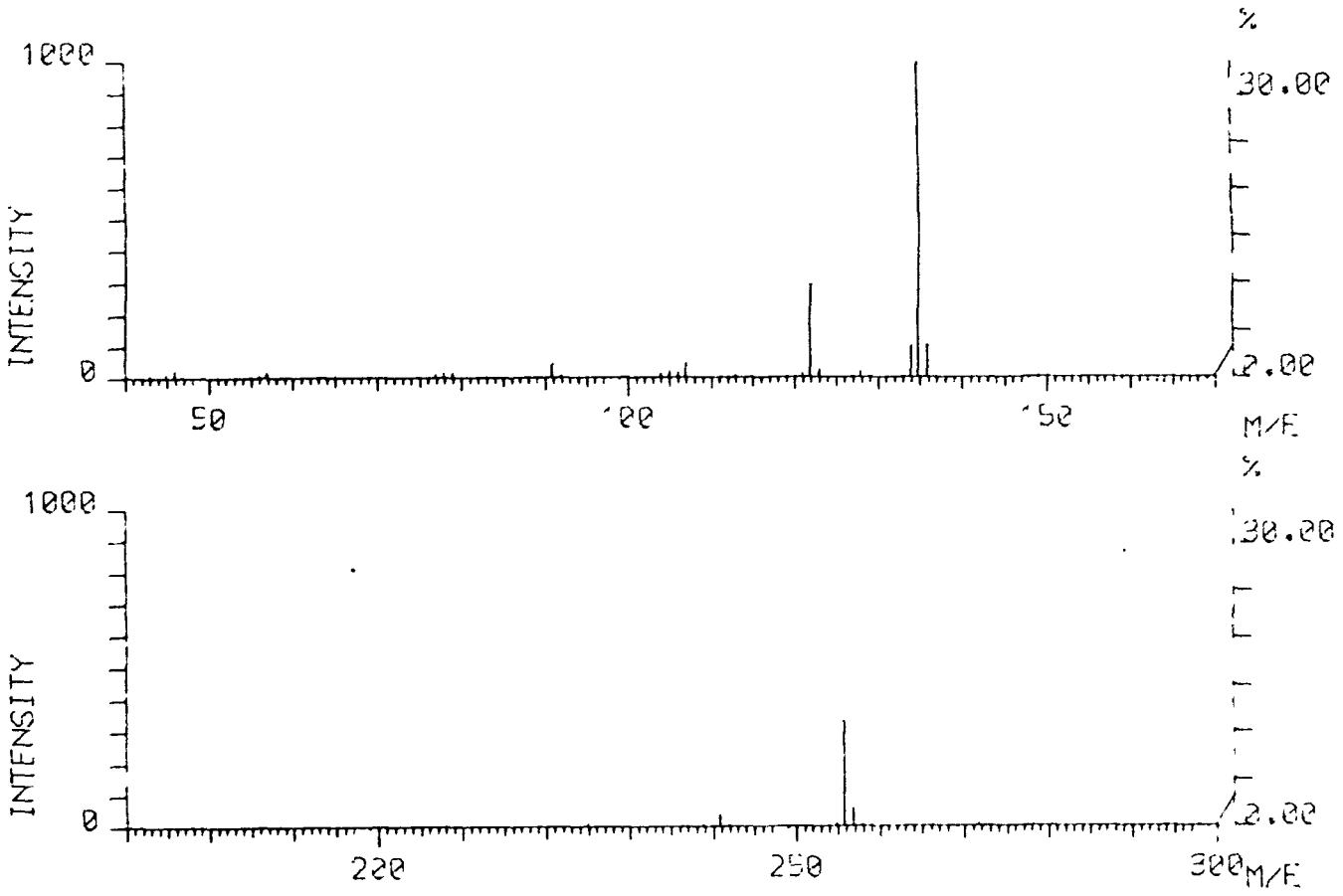

1000
INTENSITY
0
50
100
150
%
30.00
2.00
M/E
1000
INTENSITY
0
200
250
300
%
30.00
2.00
M/E

Fig. 8

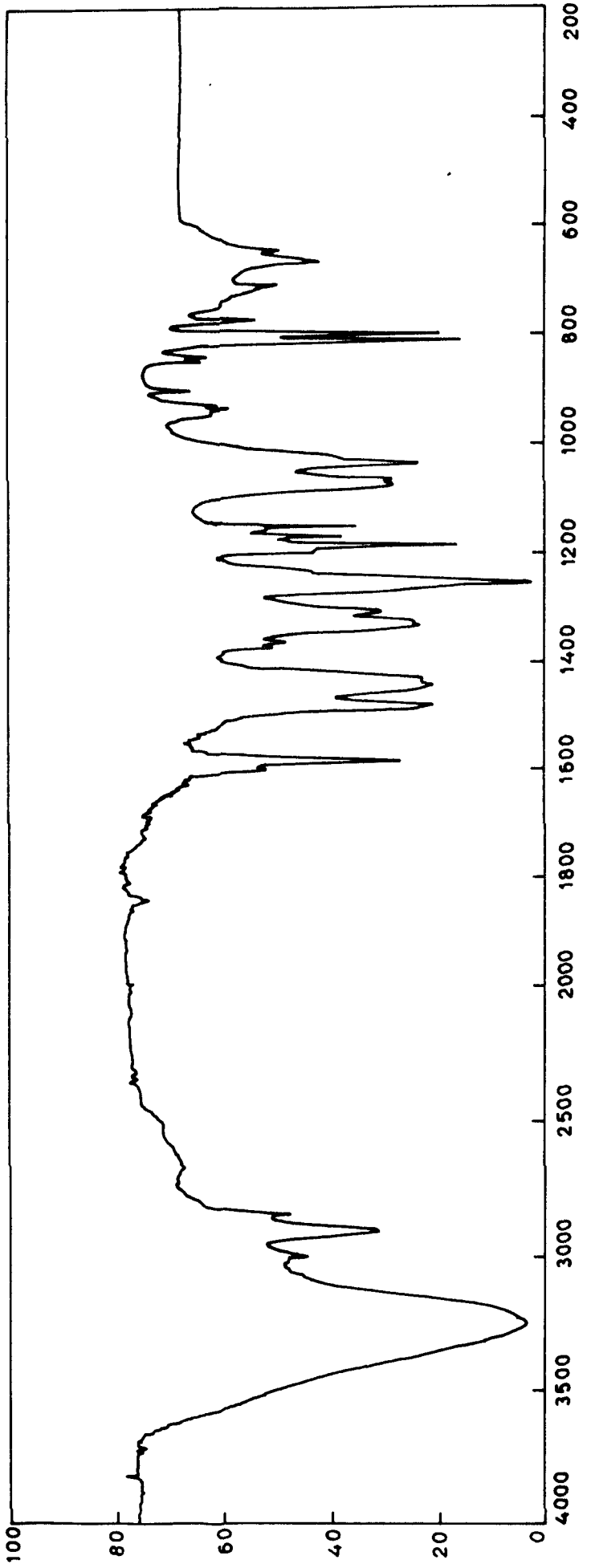

100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200

FIG. 9

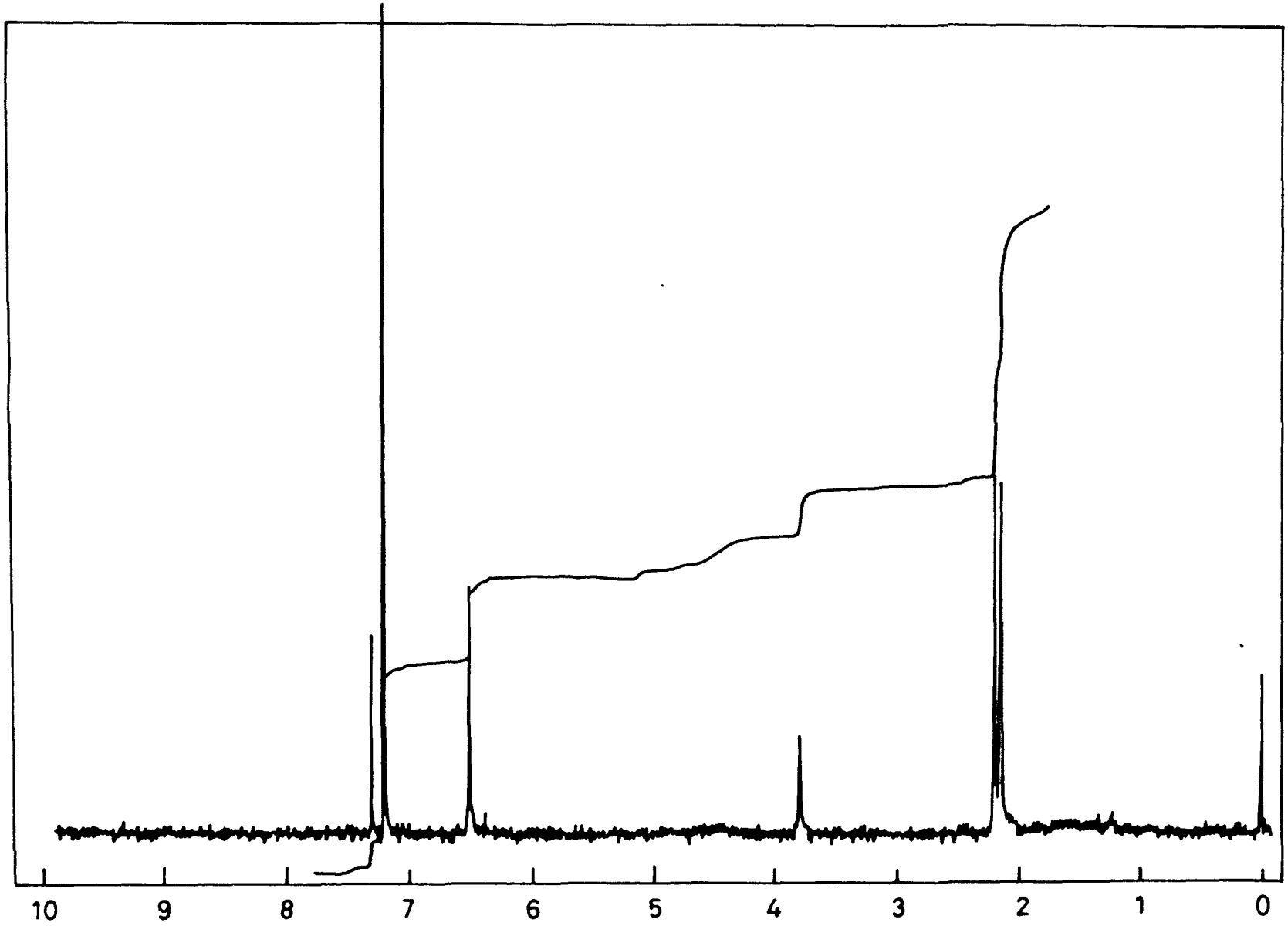


FIG. 10

Table IV

Chemical shifts of protons of 6-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVII)

Proton assignment	Chemical shifts (∂ ppm)
CH_3-2,3'	2.15 (s, 6H)
CH_3-3,4'	2.20 (s, 6H)
-CH_2-	3.81 (s, 2H)
H-4,5,5',6'	6.54 (s, 4H)
HO-1,2'	7.35 (s, 2H)

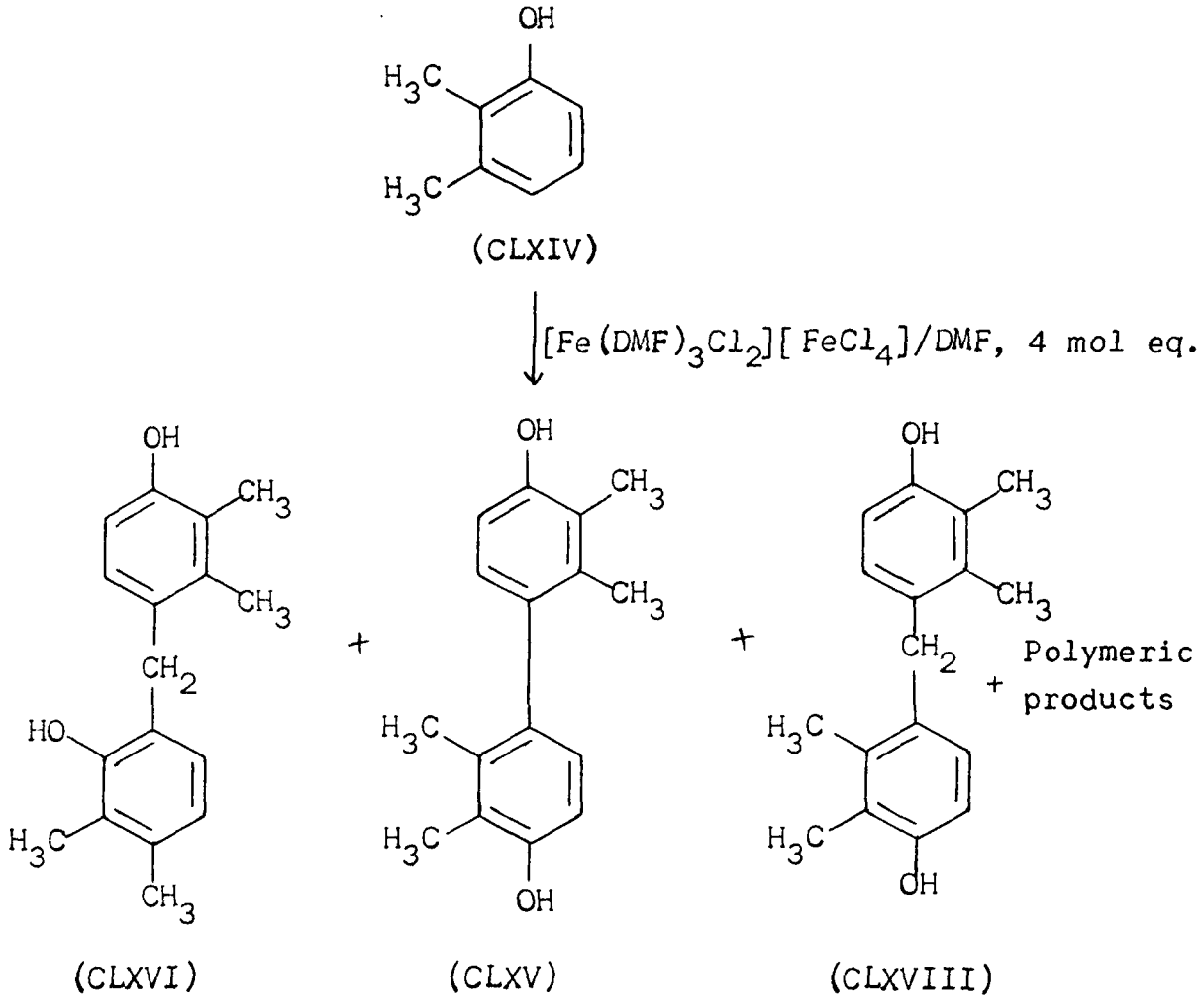
s= singlet; spectrum run in $CDCl_3$ at 90 MHz; TMS as internal standard ∂= 0.00 ppm.

Reaction of 2,3-dimethylphenol with $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in homogeneous medium in the molar ratio 1:4

In an attempt to improve the yields of the dimeric products, the reaction of 2,3-dimethylphenol with $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in the molar ratio 1:4 was also studied. The reaction was performed in the previously described manner. The reaction on usual work up and chromatographic purification yielded, besides unreacted starting material, three products. Of the three, two products were found identical in all respects (m.m.p., i.r., n.m.r. and mass) to authentic samples of 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) and 4-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVI), while the third product melting at 145-6°C was partially characterized, with the help of i.r. and mass spectra, as 4-[4'-hydroxy-2',3'-dimethylbenzyl]-2,3-dimethylphenol (CLXVIII). A mixture of polymeric products which could not be further purified even on repeated column chromatography was also obtained.

The compound melting at 145-6°C gave positive alcoholic $FeCl_3$ test indicating the presence of phenolic group. Its i.r. spectrum (Fig. 11) further confirmed the presence of hydroxy group by exhibiting a band at 3380 cm^{-1}. The mass spectrum (Fig. 12) which was almost identical to those of diarylmethanes (CLXVI) and

(CLXVII) exhibited, beside molecular ion peak at m/z 256, two prominent peak at m/z 122 and 135. These peaks can be attributed to the ions formed by fission of diarylmethane linkage. The peaks at m/z 91 and 107 were less intense. It can be said, on the basis of i.r. and mass spectral data, that the compound is a diarylmethane. The compound was, therefore, characterized as 4-[4'-hydroxy-2',3'-dimethylbenzyl]-2,3-dimethylphenol (CLXVIII).



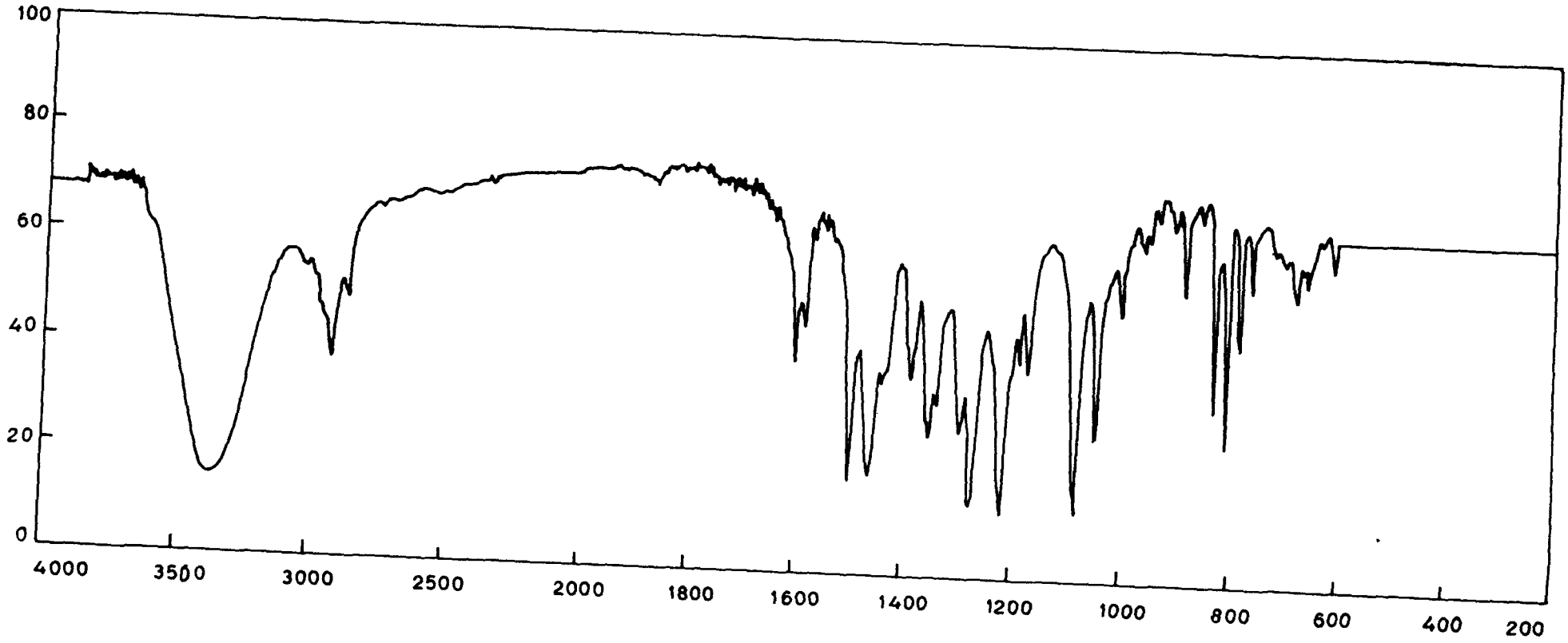

100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200

FIG. 11

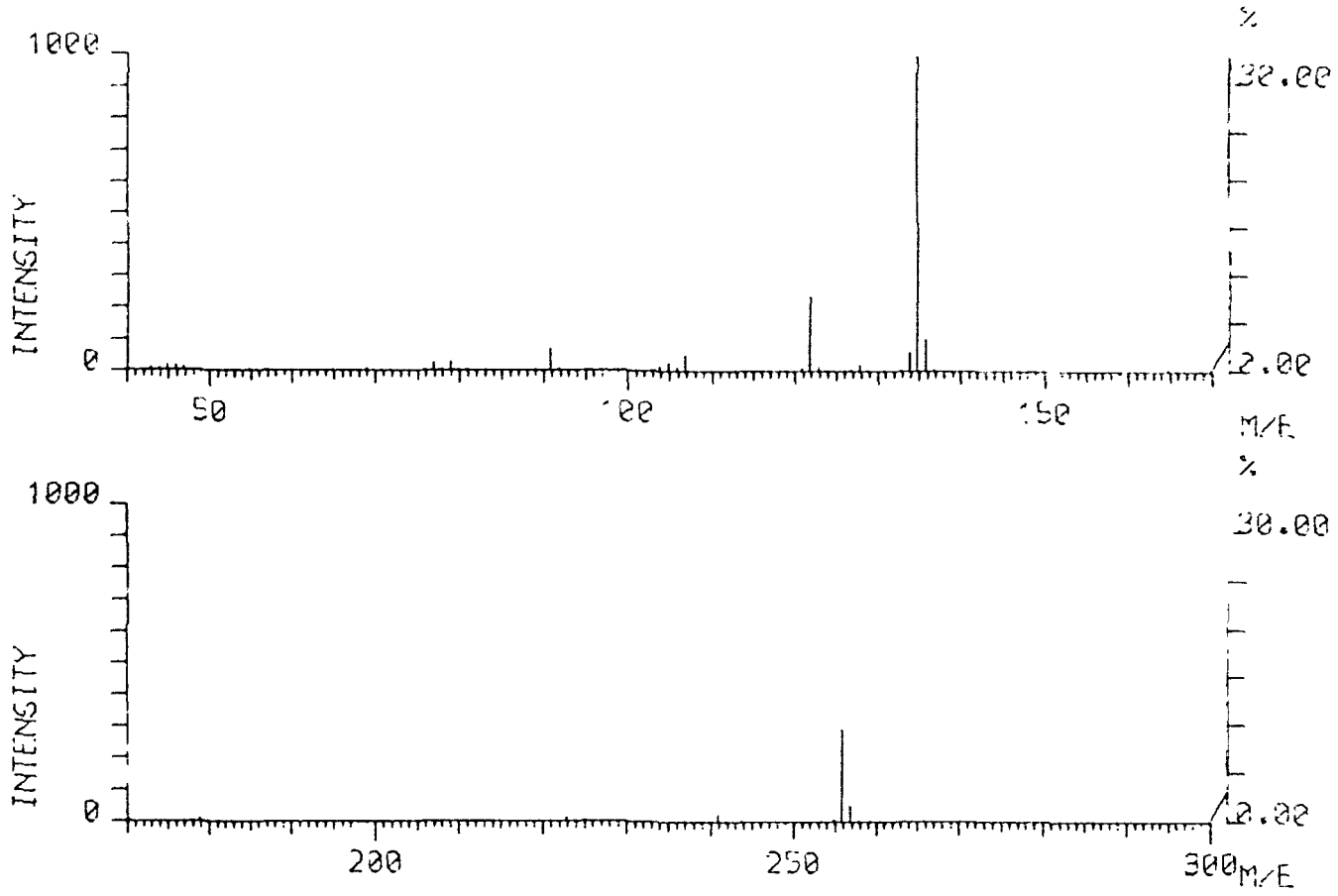
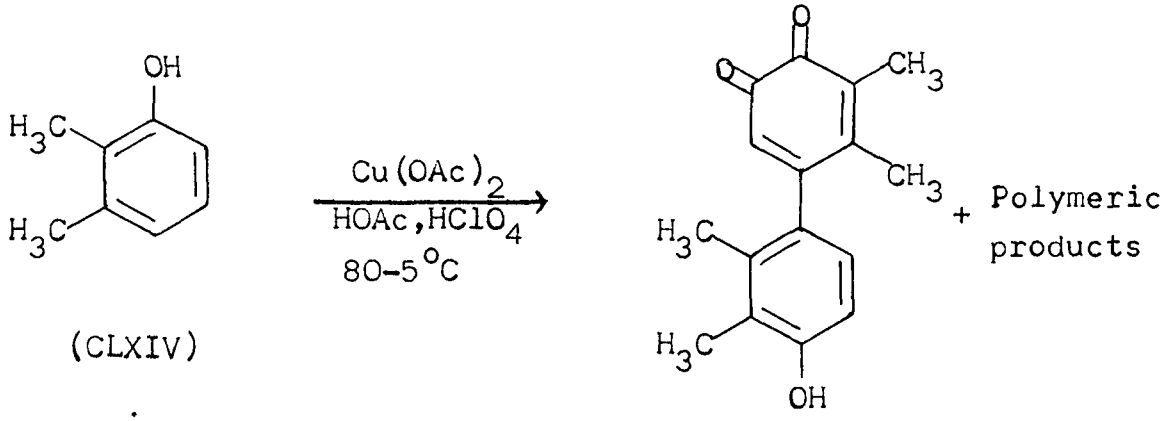

1000
INTENSITY
0
50
100
150
%
30.00
2.00
M/E
1000
INTENSITY
0
200
250
300
%
30.00
2.00
M/E

Fig. 12

Reaction of 2,3-dimethylphenol with copper(II) acetate in the presence of perchloric acid

The reaction was performed in the following manner. To a mixture of 2,3-dimethylphenol, copper(II) acetate and acetic acid, were added few drops of perchloric acid. The resulting mixture was stirred at 80-5°C for 24 hours. The contents were cooled down to room temperature and poured into water. The organic material was extracted with ether. The ethereal layer was washed with water and evaporated to give a crude solid which was subjected to column chromatography on silica gel. After the recovery of the starting material, a bright red solid was obtained on elution with petrol: benzene (1:1) which was crystallized from petrol-benzene mixture as red crystals, m.p.172-5°C. This compound was characterized as 5-[4'-hydroxy-2',3'-dimethylphenyl]-3,4-dimethyl-1,2-benzoquinone (CLXIX). A polymeric tar was obtained when the column was eluted with benzene, ethyl acetate and methanol.



(CLXIV)

(CLXIX)

Characterization of 5-[4'-hydroxy-2',3'-dimethylphenyl]-3,4-dimethyl-1,2-benzoquinone (CLXIX)

The compound melting at 172-5°C exhibited, in the mass spectrum (Fig. 13), the molecular ion peak at m/z 256 suggesting it to be a dimeric product. Its ultra-violet spectrum showed maxima at 253 and 398 nm indicating the presence of benzoquinone moiety. Infra-red spectrum (Fig. 14) displayed hydroxyl stretching band at 3480 cm^{-1}, while the carbonyl band was observed at 1640 cm^{-1}. The structure of this compound was further elucidated with the help of ^{1}H-n.m.r., mass and ^{13}C-n.m.r. spectra. ^{1}H-n.m.r. spectrum (Fig. 15) displayed singlets at δ 2.03, 2.07 and 2.18 integrating for 3,6 and 3 protons, respectively. These signals were attributed to four methyl groups. Another singlet at δ 4.95 for one proton which disappeared on shaking with D_2O was assigned to the phenolic proton. Two ortho-coupled doublets at δ 6.62 and 6.80 (J=8 Hz), each for one proton, were imputed to aromatic protons of the phenol unit. Aromatic region of the spectrum displayed a singlet at δ 6.60 for one proton. This signal was ascribed to the proton on the benzoquinone unit. The chemical shift data of compound (CLXIX) is shown in table V.

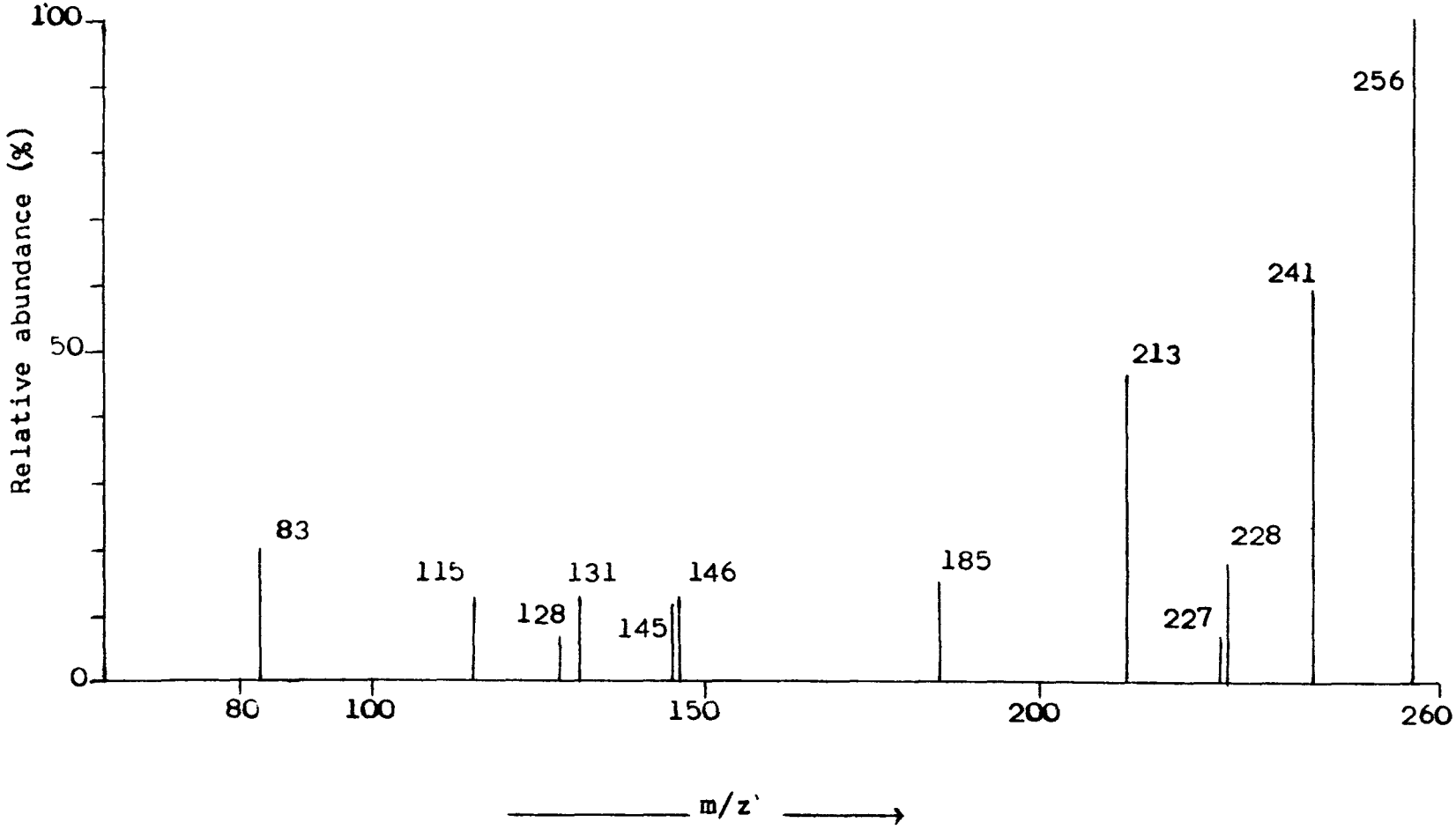

100
50
0
Relative abundance (%)
83
115
128
131
145
146
185
213
227
228
241
256
80
100
150
200
260
m/z

Fig. 13

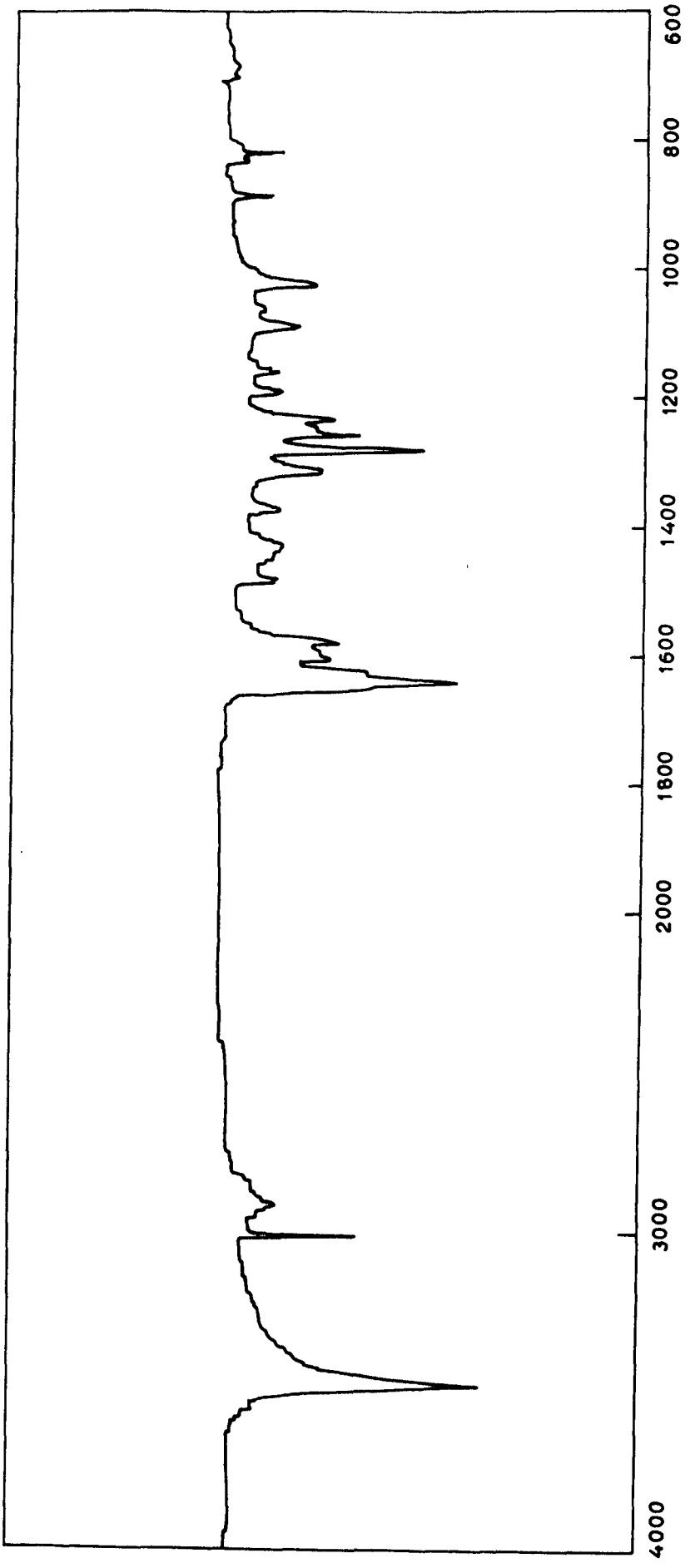


FIG. 14

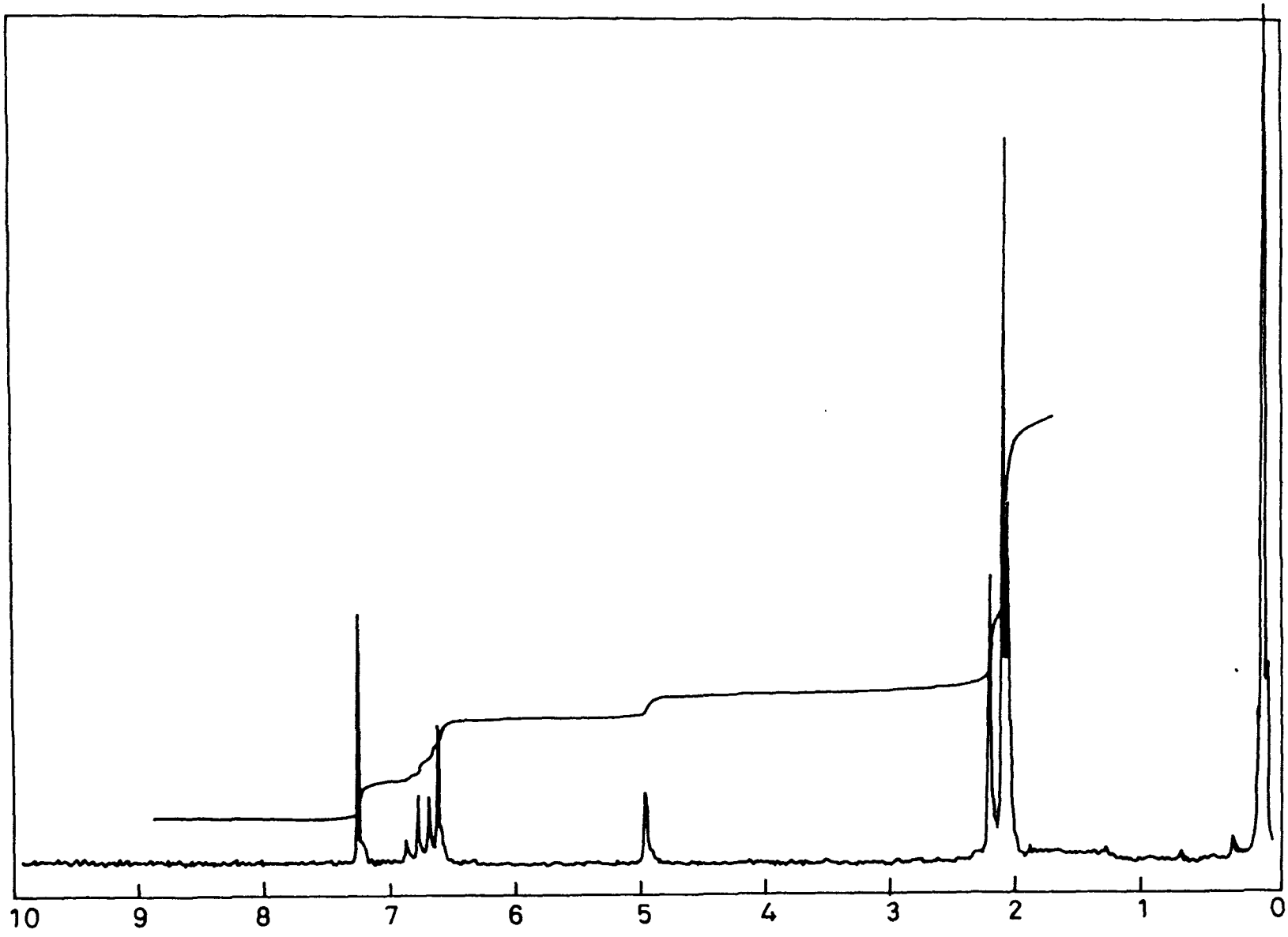


FIG. 15

Table V

Chemical shifts of protons of 5-[4'-hydroxy-2',3'-dimethylphenyl]-3,4-dimethyl-1,2-benzoquinone (CLXIX).

Proton assignment	Chemical shifts (∂ ppm)
CH_3-3'	2.03 (s, 3H)
CH_3-2',4	2.07 (s, 6H)
CH_3-3	2.18 (s, 3H)
HO-4'	4.95 (s, 1H)
H-6	6.60 (s, 1H)
H-5'	6.62 (d, J=8 Hz, 1H)
H-6'	6.80 (d, J=8 Hz, 1H)

s= singlet, d= doublet; spectrum run in $CDCl_3$ at 90 MHz; TMS as internal standard ∂= 0.00 ppm.

Mass spectrum exhibited the molecular ion peak as the base peak. The loss of a methyl radical from the $M^{+\cdot}$ gave an intense ion at m/z 241. The peaks at m/z 228 and 227 can be attributed to the loss of CO and CHO species. The loss of a methyl group for the fragment at m/z 228 gave an ion at m/z 213. The peak at m/z 185 may be attributed to the loss of two carbon monoxide molecules and a methyl radical. Two structurally

diagnostic peaks were seen at m/z 146 and 145. The fragment at m/z 146 loses a methyl radical to give an ion at m/z 131, while the peak at m/z 115 may be attributed to the loss of two methyl radicals from the ion at m/z 145. An ion at m/z 83 may be derived from the benzoquinone unit (Chart I). It can be said on the basis of above data that the compound is a dimer whose one unit is 2,3-dimethylphenol and the other being dimethylbenzoquinone. The linkage of the phenol unit through para-position was confirmed by the negative Gibb's test. The compound was characterized, in the light of plausible mechanism, as 5-[4'-hydroxy-2',3'-dimethyl-phenyl]-3,4-dimethyl-1,2-benzoquinone (CLXIX).

The structure of the compound was further supported by ^{13}C-n.m.r. spectrum (Fig. 16). The chemical shift values for ^{13}C are given in table VI. The signals at ð 186.87 and 187.84 supported the presence of two carbonyl groups. A signal at ð 154.46 was assigned to the carbon attached to the hydroxy group. Signals for the four methyl groups were observed in the region ð 11.81-18.31, while the signals for the nine aromatic carbons appeared in the region ð 112.42-148.73.

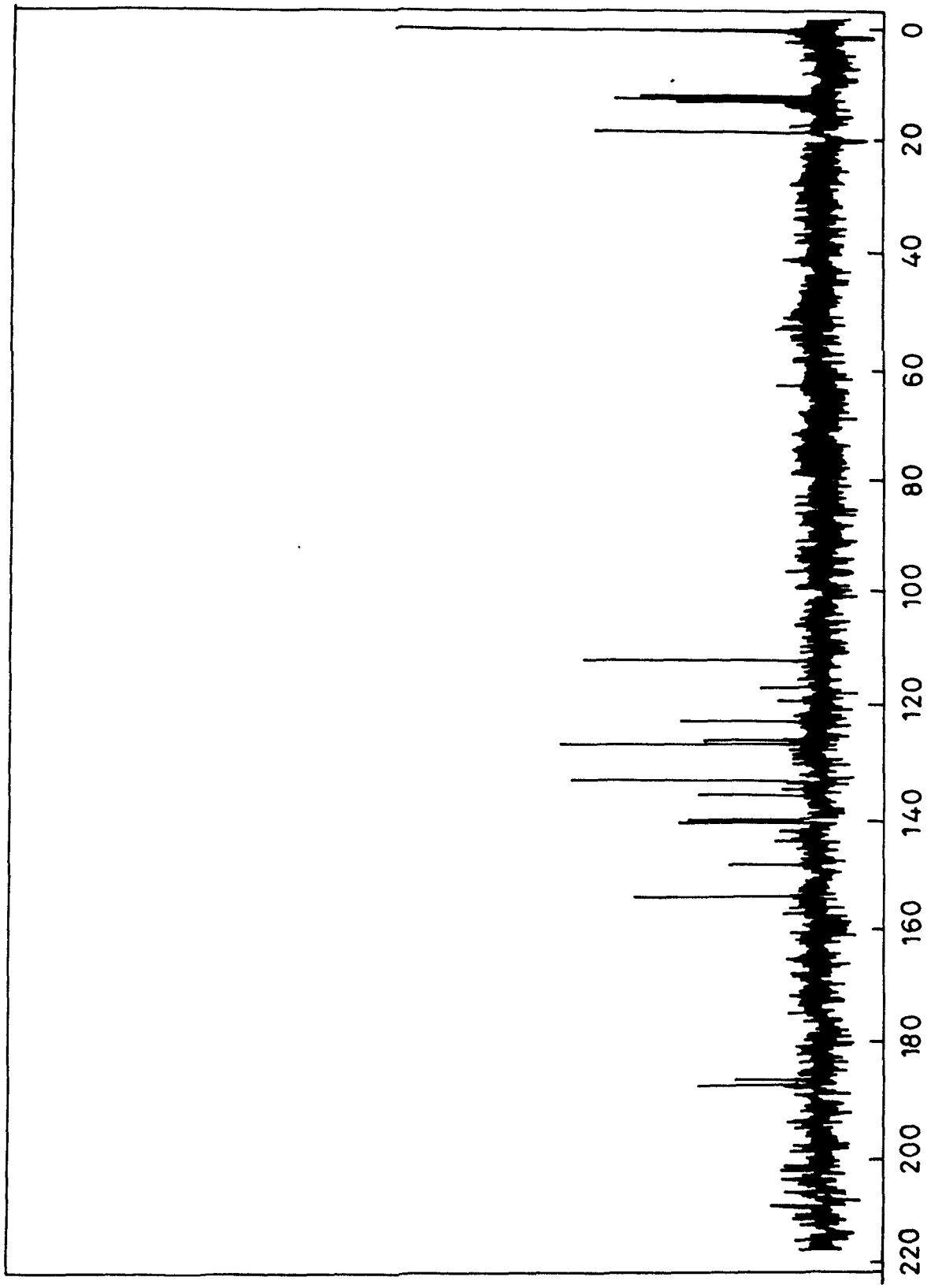


FIG. 16

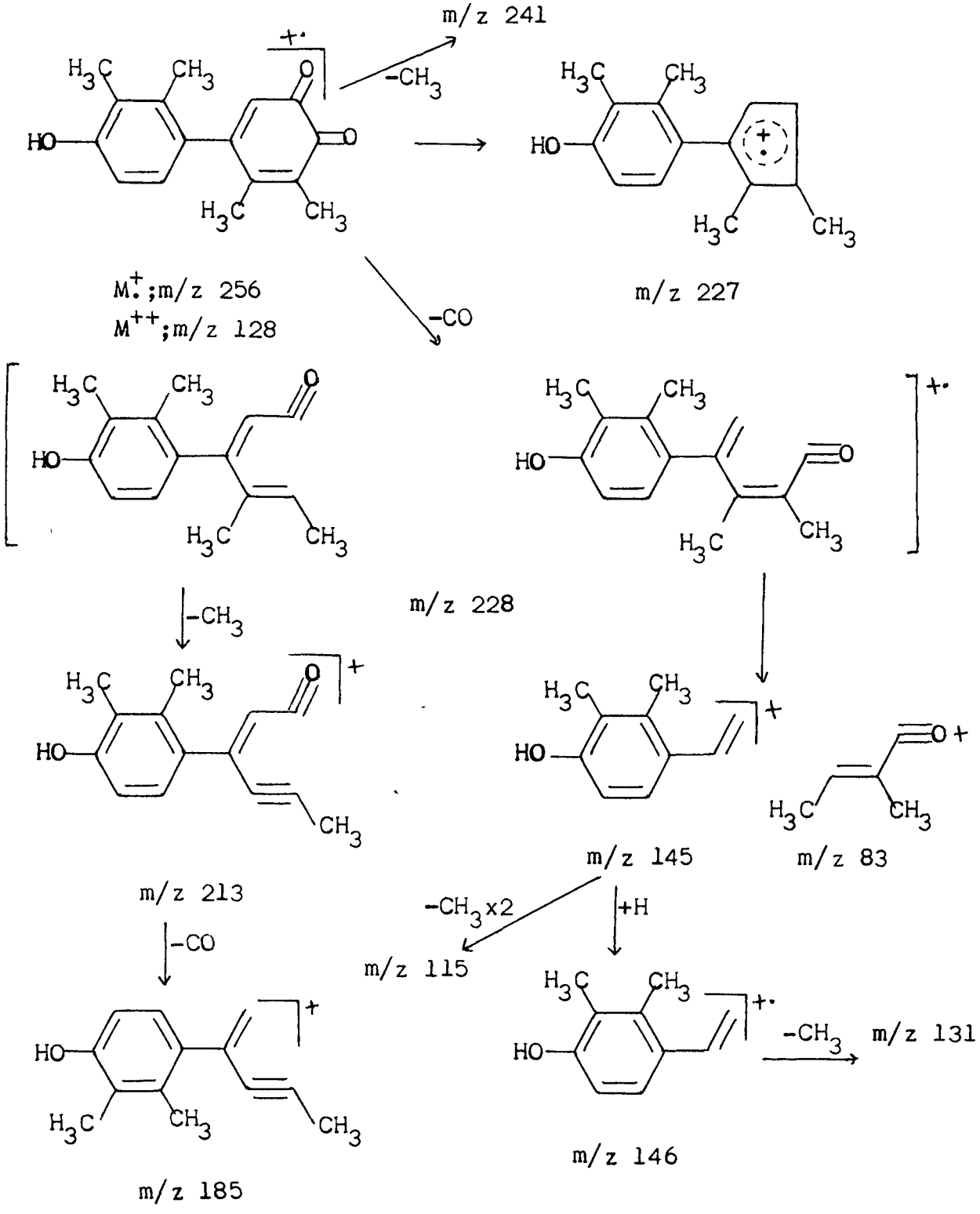

m/z 241
-CH3
M+.;m/z 256
M++;m/z 128
m/z 227
-CO
m/z 228
-CH3
m/z 213
-CO
m/z 185
m/z 145
m/z 83
-CH3x2
+H
m/z 115
-CH3
m/z 131
m/z 146

Chart I

Table VI

Chemical shifts of carbons of 5-[4'-hydroxy-2',3'-dimethylphenol]-3,4-dimethyl-1,2-benzoquinone (CLXIX).

Carbon assignment	Chemical shifts (∂ ppm)
CH_3-3'	11.81
CH_3-3	12.19
CH_3-2'	12.68
CH_3-4	18.31
C-5'	112.42
C-3'	123.37
C-6'	126.62
C-1'	127.38
C-5	133.99
C-2'	136.59
C-3	140.81
C-4	141.20
C-6	148.73
C-4'	154.46
C-1	186.87
C-2	187.84

Spectrum run in $CDCl_3$ at 90 MHz; TMS as internal standard ∂= 0.00 ppm.

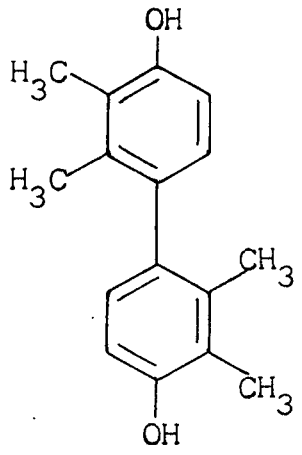
The results of the oxidation studies on 2,3-dimethylphenol can be summarized as follows.

Polymeric products were obtained in major amount in all the experiments. In the reaction of 2,3-dimethylphenol (CLXIV) with silica bound ferric chloride, 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) was the only dimeric product. Oxidation with $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in the heterogeneous medium gave only p-p coupled biphenol (CLXV), while in the homogeneous medium diarylmethane derivatives were also obtained besides p-p coupled biphenol (CLXV). Oxidation with copper(II) acetate in the presence of perchloric acid in acetic acid furnished only 5-[4'-hydroxy-2',3'-dimethylphenyl]-3,4-dimethyl-1,2-benzoquinone (CLXIX).

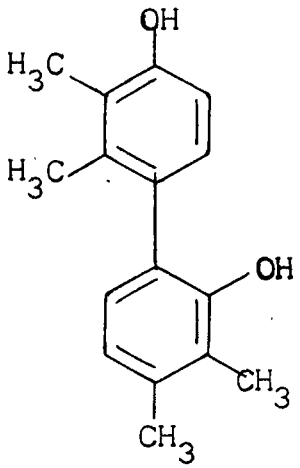
It is evident from these results that in all the experiments, except that with $Cu(OAc)_2$-$HClO_4$-HOAc reagent system, the major product was 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) and no o-p or o-o coupled biphenol was obtained, in any case.

The formation of 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CXLV) can be explained by radical pairing of aryloxy radicals. 2,3-Dimethylphenol has free ortho and para positions and hence can give three biphenolic C-C coupled products (CLXV, CLXX, CLXXI).and two C-O dimers (CLXXII) and (CLXXIII). One

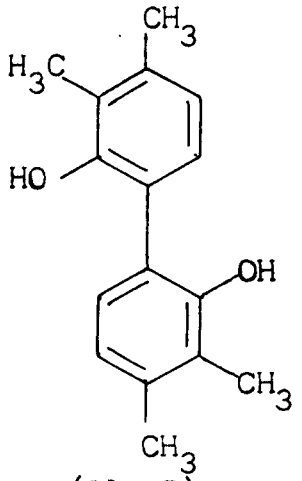
apparent anamalous result is the formation of para-para coupled product (CLXV) from the oxidation of 2,3-dimethylphenol with silica bound ferric chloride and $[Fe(DMF)_3Cl_2][FeCl_4]$ complex.



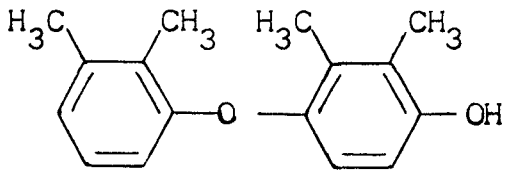
(CLXV)



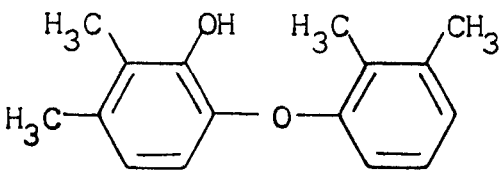
(CLXX)



(CLXXI)



(CLXXII)

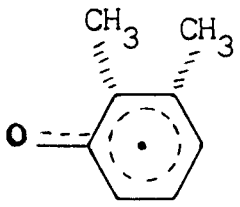


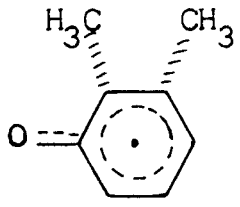
(CLXXIII)

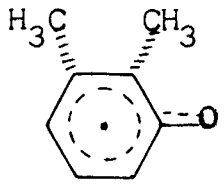
A detailed study on the role of steric effects in the oxidation of methyl-substituted phenols has recently been carried out by Armstrong and co-workers[60]. They have postulated that the coupling of phenoxy radicals proceeds by a staggered sandwich transition state and when more than one such transition states can be considered, reaction proceeds preferentially via the

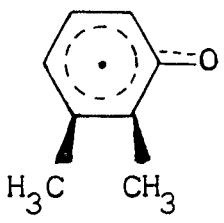
transition state possessing the smallest number of non-bonded interactions between the methyl groups of the radicals undergoing coupling.

There are three possible modes of approach of the 2,3-dimethylphenoxy radicals to give dimers: Staggered, eclipsed and head-to-tail. However, there are two possible head-to-tail geometries of approach, (CLXXIV) and (CLXXV), for the coupling of phenoxy radicals. The less hindered and energetically more favoured configuration (CLXXV) could lead to the para-C-O coupled product (CLXXII). It is probably due to this favourable approach that polymeric products, which are believed to be polyethers, are formed in major amount in these reactions.





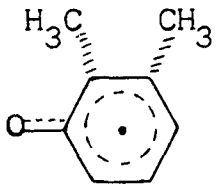


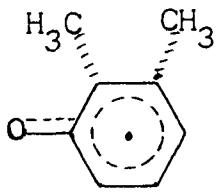


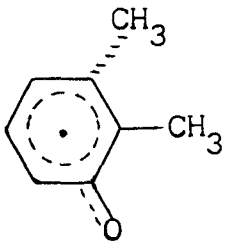
(CLXXIV)

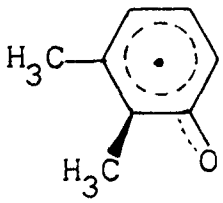
(CLXXV)

There are also two possible staggered geometries of approach (CLXXVI) and (CLXXVII) for the coupling of 2,3-dimethylphenoxy radicals. The more favoured approach (CLXXVII), in which there are no methyl-methyl interactions, would lead to the ortho-para coupled product (CLXX) while approach (CLXXVI) would give the ortho-ortho-dimer (CLXXI).



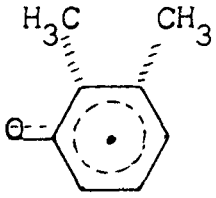


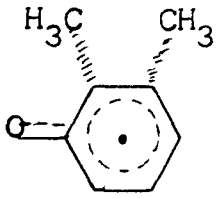


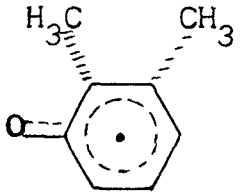


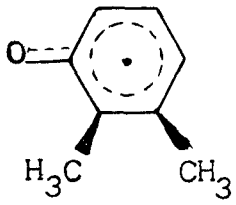
(CLXXVI) (CLXXVII)

Similarly, there are two possible eclipsed geometries of approach (CLXXVIII) and (CLXXIX) for the para-para-coupling of 2,3-dimethylphenoxy radicals, one of which (CLXXIX) possesses no methyl-methyl non-bonded interactions. The preferential formation of para-para coupled dimer (CLXV) in the oxidation of 2,3-dimethylphenol can be explained by the approach (CLXXIX).









(CLXXVIII) (CLXXIX)

Of all the possible approaches, three approaches (CLXXV, CLXXVII, CLXXIX) will be energetically more favourable. The head-to-tail geometry of approach (CLXXV) seems most favourable as there will be no interaction between the substituents on the two phenoxy radicals. This is in good agreement with the experimental results as the large amount of polymeric products are obtained. There will be no interactions between the substituents on the two radicals in the eclipsed geometry of approach (CLXXIX). This is also in good agreement with the experimental results. However, ortho-para-coupled product (CLXX), which can be expected from the staggered geometry of approach (CLXXVII), was not obtained. This

can be attributed to the interaction between the oxygen atom and the methyl group which probably makes this approach less favourable.

The mechanism for the formation of diarylmethane derivatives (CLXVI-CLXVIII) in the reaction of 2,3-dimethylphenol with $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in DMF is not clear. The formation of related diarylmethane derivatives in the oxidation of alkylbenzenes has been explained by the disproportionation of the methyl group in methylbenzenes[29]. However, such a mechanism seems not feasible in our case. It is assumed that the methylene species probably derives either from DMF or $[Fe(DMF)_3Cl_2][FeCl_4]$ complex, but the mechanism is not fully understood.

The mechanism for the formation of 5-[4'-hydroxy-2',3'-dimethylphenyl]-3,4-dimethyl-1,2-benzoquinone (CLXIX) by the oxidation of 2,3-dimethylphenol with copper(II) acetate in the presence of perchloric acid in acetic acid is also not fully understood. The formation of (CLXIX) can be explained in terms of either oxidation of 2,3-dimethylphenol to 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) followed by oxygenation of one unit or by the initial formation of orthoquinone which may couple with 2,3-dimethylphenol[61,62]. However, since no intermediate could be isolated, the exact path of the reaction can not be assigned.

EXPERIMENTAL

All the melting points were recorded on Kofler microscopical hot stage and are uncorrected. Thin layer chromatography was performed on silica gel G of BDH grade. The spots were developed either by spraying with alcoholic ferric chloride solution or by iodine vapours. All the reagents were used of BDH grade without further purification. 2,3-Dimethylphenol was of BDH grade and was crystallized from petrol before use. Infra-red spectra were recorded on a Pye Unicam SP3-100 spectrophotometer. Ultra-violet spectrum was obtained on a Pye Unicam PU8800 instrument. Nuclear magnetic resonance spectra were recorded on 60 MHz Varian A60D, 80 MHz Varian CFT-20 or 90 MHz FX-90 instruments using tetramethylsilane (TMS) as internal standard. All the chemical shift values are given in ppm downfield from TMS (δ= 0). The abbreviations, 's and d' denote singlet and doublet, respectively. Mass spectra were recorded with JEOL JMS-D300 spectrometer at 70 eV.

Preparation of silica bound ferric chloride

Silica bound ferric chloride was prepared according to Jempty and Miller procedure[52]. Ferric chloride was dissolved in 95% absolute diethyl ether (5% absolute methanol). This was added to a weighed amount of oven dried (150°C) chromatographic grade silica gel (60-120 mesh). The solvent was removed on a rotary

evaporator, and the reagent activated at 80°C for 4 hours. The reagent so produced was a free floating yellow powder which was moisture and light sensitive.

Preparation of $[Fe(DMF)_3Cl_2][FeCl_4]$ complex

The reagent was prepared according to Tobinaga and Kotani's method.[36] Ferric chloride (163 g, 1 mol) was dissolved in dry ether (1.6 litre). N,N-Dimethylformamide (110 g, 1.5 mol) was then added slowly to the stirring solution of ferric chloride. A yellowish green precipitate settled in the round bottom flask which was filtered, washed with ether and dried. The powder was then crystallized from ethanol-methylene chloride to give needles of $[Fe(DMF)_3Cl_2][FeCl_4]$ complex (255 g), m.p.218-9°C (lit.[36] m.p.220°C).

Reaction of 2,3-dimethylphenol with silica bound ferric chloride

The reaction was performed by adding a solution of 2,3-dimethylphenol (CLXIV) (2 g, 16.37 mmol) in dichloromethane (125 ml) to ferric chloride (5.31 g, 32.74 mmol) adsorbed on silica gel (53.10 g). An immediate colour change was observed. The solvent was evaporated on a rotary evaporator and the resulting mixture left stirring at room temperature for two hours. Ether (200 ml) and water (100 ml) were then added. The contents were stirred and filtered. Aqueous layer was removed and the ethereal

layer washed with water till the aqueous layer was neutral to litmus and colourless. Ethereal layer was then dried over anhydrous sodium sulphate and evaporated to give a brown solid (1.93g). T.l.c. examination of this crude mass, using benzene as the developer, displayed an elongated spot alongwith a trailing. The crude solid was subjected to column chromatography over a silica gel column. Unchanged 2,3-dimethylphenol (750 mg) was recovered when the column was eluted with petrol and petrol:benzene (9:1). Further elution of the column with petrol:benzene (3:17) yielded a solid which was crystallized from petrol-methanol mixture to give white crystals of 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) (75 mg), m.p.192-4°C. Furthermore elution of the column with more polar eluents such as benzene and ethyl acetate furnished a complex mixture of polymeric products (780 mg) which could not be purified even on repeated column chromatography.

4,4'-Dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV)

IR(KBr) : $\nu_{max.}$ 3320, 3000, 2940, 1580, 1440, 1380, 1345, 1270, 1200, 1180, 1130, 1060, 1035, 910, 810, 800, 740, 670 cm^{-1}.

NMR($CDCl_3$) : δ 1.95 (s, 6H, CH_3-2,2'), 2.22 (s, 6H, CH_3-3,3'), 4.64 (s, 2H, HO-4,4'), 6.63 (d, J=9 Hz, 2H, H-6,6'), 6.81 (d, J=9 Hz, 2H, H-5,5').

MS(rel. int.) : m/z 243 (18.12), 242 (100), 241 (8.89), 228 (6.71), 227 (38.88), 226 (9.02), 225 (6.48), 213 (7.87), 212 (32.88), 211 (8.98), 197 (6.16), 121 (6.76), 106 (7.00).

When 2,3-dimethylphenol (CLXIV) (10 g, 81.8 mmol) was treated with ferric chloride (2.66 g, 16.37 mmol) adsorbed on silica gel (26.6 g) under almost identical conditions as described in the preceding experiment. The reaction on usual work up and chromatographic purification yielded a white product which was crystallized from petrol-methanol mixture to give crystals of 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) (86 mg), m.p.192-4°C. Further elution of the column with petrol-benzene, benzene and benzene-ethyl acetate mixture yielded a mixture of polymeric products (450 mg) which could not be purified.

Reaction of 2,3-dimethylphenol with $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in heterogeneous medium

The reaction was performed in the following manner. To a solution of the iron complex (44.49 g, 81.8 mmol) in 200 ml of water, 2,3-dimethylphenol (5 g, 40.92 mmol) dissolved in 100 ml of ether was added. The reaction mixture was left stirring for eight hours at room temperature. Aqueous layer was then removed, ethereal layer washed with water, dried over sodium sulphate and

evaporated to dryness to give a crude product (4.4 g) which was subjected to column chromatography on silica gel. Elution of the column with petrol afforded unchanged 2,3-dimethylphenol (2.900 g). Further elution of the column with petrol-benzene (1:4) yielded a light pink solid which on crystallization from benzene-acetone mixture gave white crystals of 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) (82 mg), m.p.192-4°C. Furthermore elution of the column with benzene-ethyl acetate (1:1) gave polymeric mixture (100 mg).

4,4'-Dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV)

NMR(DMSO-d_6) : δ 1.80 (s, 6H, CH_3-2,2'), 2.03 (s, 6H, CH_3-3,3'), 6.57 (s, 4H, H-5,5',6,6'), 8.62 (s, 2H, HO-4,4').

Reaction of 2,3-dimethylphenol with $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in homogeneous medium in the molar ratio 1:2

2,3-Dimethylphenol (5 g, 40.92 mmol) was added to a solution of $[Fe(DMF)_3Cl_2][FeCl_4]$ complex (44.49g, 81.8 mmol) in N,N-dimethylformamide (100 ml). The reaction mixture was heated at reflux temperature for ten hours. Excess of water was then added and the organic material extracted with ether. Ether layer was washed with water, dried over anhydrous sodium sulphate and evaporated to give a crude mass (4.5 g) which was chromatographed

on a silica gel column. Unchanged starting material was eluted with petrol as white solid (2.150 g). Elution of the column with petrol-benzene (2:3) furnished a white compound, crystallized from petrol-carbon tetrachloride mixture to give white crystals of 4-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVI) (29 mg), m.p.119-21°C. When the composition of the eluent was changed to petrol:benzene (1:4), a white solid was obtained which was crystallized from benzene-acetone mixture to give crystals (98 mg) of 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV), m.p.192-4°C. Further elution of the column with benzene yielded another white solid which was crystallized from petrol-benzene mixture to give crystals of 6-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVII) (9 mg), m.p.194-5°C. A mixture of polymeric products (1 g) was obtained when the column was eluted with benzene:ethyl acetate (1:1).

4-[2'-Hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVI)

IR(KBr) : ν_{max} 3340, 3010, 2940, 1585, 1480, 1460, 1440, 1390, 1380, 1350, 1275, 1210, 1180, 1135, 1060, 1035, 910, 810, 800, 750, 670, 620 cm^{-1}.

NMR($CDCl_3$) : δ 2.14 (s, 3H, CH_3-3'), 2.18 (s, 6H, CH_3-2,4'), 2.24 (s, 3H, CH_3-3), 3.87 (s, 2H, $-CH_2-$), 4.54 (s, 1H, HO-2'), 4.68 (s, 1H, HO-1), 6.56

(d, J=9 Hz, 1H, H-6), 6.68 (s, 2H, H-5',6'), 6.81 (d, J=9 Hz, 1H, H-5).

MS(rel. int.) : m/z 257 (5.58), 256 (28.94), 255 (2.25), 242 (23.58), 241 (7.12), 227 (8.86), 212 (8.08), 136 (10.00), 135 (100), 134 (12.51), 122 (32.55),

6-[2'-Hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVII)

IR(KBr) : ν_{max} 3250, 3000, 2900, 2840, 1580, 1480, 1440, 1330, 1250, 1185, 1150, 1070, 1030, 940, 900, 840, 810, 800, 770, 710, 670 cm^{-1}.

NMR($CDCl_3$) : δ 2.15 (s, 6H, CH_3-2,3'), 2.20 (s, 6H, CH_3-3,4'), 3.81 (s, 2H, $-CH_2-$), 6.54 (s, 4H, H-4,5,5',6'), 7.35 (s, 2H, HO-1,2').

MS(rel. int.) : m/z 257 (6.29), 256 (33.57), 241 (4.47), 136 (10.29), 135 (100), 134 (10.61), 122 (29.28), 107 (5.04), 91 (5.12).

Reaction of 2,3-dimethylphenol with $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in homogeneous medium in the molar ratio 1:4

The reaction was performed in the previously described manner. Thus, 2,3-dimethylphenol (5 g, 40.92 mmol) was treated

with $[Fe(DMF)_3Cl_2][FeCl_4]$ complex (89 g, 163.68 mmol) in DMF for 10 hours. The reaction on usual work up yielded a crude solid (4.2 g) which was subjected to column chromatography over silica gel. Unreacted starting material (500 mg) was eluted with petrol. Further elution with petrol:benzene (2:3) afforded 4-[4'-hydroxy-2',3'-dimethylbenzyl]-2,3-dimethylphenol (CLXVIII) which was crystallized from petroleum ether-carbon tetrachloride as white crystals (25 mg), m.p. 145-6°C. Furthermore elution with petrol: benzene (1:4) and benzene gave successively, 4-[2'-hydroxy-3',4'-dimethylbenzyl]-2,3-dimethylphenol (CLXVI) (28 mg) and 4,4'-dihydroxy-2,2',3,3'-tetramethylbiphenyl (CLXV) (9 mg). Furthermore elution of the column with benzene:ethyl acetate (1:1) gave a mixture of polymeric products (2.54 g).

4-[4'-Hydroxy-2',3'-dimethylbenzyl]-2,3-dimethylphenol (CLXVIII)

IR(KBr) : ν_{max} 3380, 2925, 1600, 1590, 1500, 1460, 1385, 1350, 1300, 1275, 1220, 1170, 1080, 1050, 1000, 885, 810, 785, 760, 680 cm^{-1}.

MS(rel. int.) : m/z 257 (4.78), 256 (29.58), 241 (2.38), 136 (9.52), 135 (100), 134 (7.14), 122 (23.80), 107 (4.76), 91 (7.14).

Reaction of 2,3-dimethylphenol with copper(II) acetate in presence of perchloric acid

2,3-Dimethylphenol (2 g, 16.37 mmol) was added to a stirred solution of copper(II) acetate (6.53 g, 32.74 mmol) in acetic acid (75 ml) containing catalytic amount of 70% perchloric acid. The mixture was stirred at 80-85°C for 24 hours. The contents were cooled down and poured into water and ether was added. The ethereal layer was washed several times with water, dried over anhydrous sodium sulphate and evaporated. The residue (1.98 g) was then chromatographed on a silica gel column. Elution of the column with petrol gave unreacted 2,3-dimethylphenol (110 mg). Further elution with petrol-benzene (1:1) afforded a pure sample of bright red coloured 5-[4'-hydroxy-2',3'-dimethylphenyl]-3,4-dimethyl-1,2-benzoquinone (CLXIX) (200 mg), m.p.172-5°C. A polymeric tar (0.952 g) was obtained when benzene, ethyl acetate and methanol were used as eluent.

5-[4'-Hydroxy-2',3'-dimethylphenyl]-3,4-dimethyl-1,2-benzoquinone (CLXIX)

IR(KBr) : ν_{max} 3480, 3010, 2920, 1640, 1580, 1480, 1430, 1370, 1310, 1280, 1260, 1235, 1190, 1160, 1090, 1030, 890, 820 cm^{-1}.

UV(Hexane) : λ_{max} 253, 398 nm.

^{1}H-NMR($CDCl_3$) : ∂ 2.03 (s, 3H, CH_3-3'), 2.07 (s, 6H, CH_3-4,2'), 2.18 (s, 3H, CH_3-3), 4.95 (s, 1H, HO-4'), 6.60 (s, 1H, H-6), 6.62 (d, J=8 Hz, 1H, H-5'), 6.80 (d, J=8 Hz, 1H, H-6').

^{13}C-NMR($CDCl_3$) : ∂ 11.81 (CH_3-3'), 12.19 (CH_3-3), 12.68 (CH_3-2'), 18.31 (CH_3-4), 112.42 (C-5'), 123.37 (C-3'), 126.62 (C-6'), 127.38 (C-1'), 133.99 (C-5), 136.59 (C-2'), 140.81 (C-3), 141.20 (C-4), 148.73 (C-6), 154.46 (C-4'), 186.87 (C-1), 187.84 (C-2).

MS(rel. int.) : m/z 256 (100), 241 (59.71), 228 (18.42), 227 (7.49), 213 (46.29), 185 (15.14), 146 (13.65), 145 (12.03), 131 (13.22), 128 (7.19), 115 (13.09), 83 (20.36).

BIBLIOGRAPHY

1. W.I. Taylor and A.R. Battersby, 'Oxidative coupling of phenols', Marcel Dekker, Inc., New York (1967) (a) p.95, (b) p.1.

2. L. Merlini and A. Zanarotti, J. Chem. Soc. Chem. Commun., 695 (1979).

3. A. Zanarotti, Tetr. Lett., 3963 (1982).

4. W.A. Waters, 'Mechanism of oxidation of organic compounds', Methuen and Co. Ltd., London (1964) (a) p.15, (b) p.145, (c) p.147.

5. A.I. Scott, Quart. Rev.(London), 19, 1 (1965).

6. T.H. Chan and P. Brownbridge, J. Chem. Soc. Chem. Commun., 20 (1981).

7. R.J. Molyneux, A.C. Waiss and W.F. Habdon, Tetrahedron, 26, 1409 (1970).

8. C.G. Haynes, A.H. Turner and W.A. Waters, J. Chem. Soc., 2823 (1956).

9. K. Bowden and C.H. Reece, J. Chem. Soc., 2249 (1950).

10. H. Erdtman, Biochem. Z., 258, 172 (1933).

11. E. Muller, H.D. spanagel and A. Rieker, Ann., 681, 141 (1965).

12. D.F. De Tar and R.A.J. Long, J. Amer. Chem. Soc., 80, 4742 (1958); E.L. Eliel, S. Meyerson, Z. Welvart and S.H. Wilen, J. Amer. Chem. Soc., 82, 2936 (1960).

13. K. Dimroth, W. Umbach and H. Thomas, Ber., 100, 132 (1967).

14. E.I. Heiba, R.M. Dessau and W.J. Koehl Jr., J. Amer. Chem. Soc., 91, 6830 (1969).

15. R.M. Dessau, S. Shihs and E.I. Heiba, J. Amer. Chem. Soc., 92, 412 (1970).

16. P.J. Andrulis Jr., M.J.S. Dewar, R. Dietz and R.L. Hunt, J. Amer. Chem. Soc., 88, 5473 (1966).

17. E.I. Heiba, R.M. Dessau and W.J. Koehl Jr., J. Amer. Chem. Soc., 91, 138 (1969).

18. R.O.C. Norman, C.B. Thomas and J.S. Willson, J. Chem. Soc., (B), 518 (1971).

19. R. Evander Ploeg, R.W. de Korte and É.C. Kooyman, J. Ctalysis, 10, 521 (1968).

20. A. Onopehenko and J.G.D. Schultz, J. Org. Chem., 37, 1414 (1972).

21. E.I. Heiba, R.M. Dessau and W.J. Koehl Jr., J. Amer. Chem. Soc., 90, 1082 (1968).

22. R.J. Quellette, in 'Oxidation in organic chemistry', W.S. Trahanovsky (Ed.), Part (B), Academic Press, New York and London (1973), p.135.

23. P.M. Maitlis, 'The organic chemistry of palladium', Vol.I and II, Academic Press, New York and London (1971).

24. D.R. Harvey and R.O.C. Norman, J. Chem. Soc., 4860 (1964).

25. S. Kazuo, I. Soturo and S. Yukitoni, Chem. Lett., 37 (1983).

26. K. Nyberg, Chem. Scripta., 120 (1974).

27. K. Nyberg and L.G. Wistrand, Chem. Scripta., 234 (1974).

28. K. Nyberg and L.G. Wistrand, J. Org. Chem., 43, 2615 (1978).

29. S. Uemura, S. Tanaka and M. Okano, J. Chem. Soc., 1966 (1976).

30. K. Nyberg and L.G. Wistrand, Acta. Chem. Scand., B-31, 731 (1977).

31. S. Tanaka, S. Uemura and M. Okano, J. Chem. Soc., 431 (1978).

32. R.O.C. Norman, C.B. Thomas and J.C. Willium, J. Chem. Soc., 325 (1973).

33. B. Enrico and M. Luigi, J. Org. Chem., 45, 3906 (1980).

34. K. Nyberg, Chem. Scripta., 115 (1974).

35. G.W.K. Cavill, E.R. Cole, P.T. Gilham and D.J. McHuge, J. Chem. Soc., 2785 (1954).

36. S. Tobinaga and E. Kotani, J. Amer. Chem. Soc., 94, 309 (1972).

37. W.W. Kaeding, J. Org. Chem., 28, 1063 (1963).

38. S.L. Cosgrove and W.A. Waters, J. Chem. Soc., 1726 (1951).

39. E. Muller, R. Mayer, B. Narr, A. Rieker and K. Scheffler, Ann., 645, 25 (1961).

40. S.P.A. Brichima, Chem. Abstr., 94, 121092f (1981).

41. T.I. Lonshehakovo, A.G. Laikumovich, V.Kh. Kadryrova, Chem. Abstr., 97, 55398u (1982).

42. C.W. Porter and F.H. Thurber, J. Amer. Chem. Soc., 43, 1194 (1921).

43. J.F. Harrod and A. Pathak, Can. J. Chem., 58, 686 (1980).

44. I.A. Batanov, U.A. Nikiforov and V.V. Ershov, Chem. Abstr., 96, 180548y (1982).

45. B.O. Lindgren, Acta. Chem. Scand., 14, 2089 (1960).

46. J. Baltes and F. Volbert, Chem. Abstr., 51, 5736d (1957).

47. F.R. Hewgill and B.S. Middleton, J. Chem. Soc., 2914 (1965).

48. F.R. Hewgill and D.G. Hewitt, J. Chem. Soc., 3660 (1965).

49. F.R. Hewgill and D.G. Hewitt, Tetrahedron, 21, 3737 (1965).

50. E. Muller, H. Kaufmann and A. Rieker, Ann., 671, 61 (1964).

51. C.J.R. Adderley and F.R. Hewgill, J. Chem. Soc., 1434 (1968).

52. T.C. Jempty, L.L. Miller and Y. Mazur, J. Org. Chem., 45, 749 (1980).

53. S. Uemura, T. Ikeda, S. Tanaka and M. Okano, J. Chem. Soc., 2574 (1979).

54. K.K. Geogrieff, Science, 173, 537 (1972).

55. L.M. Ferguson, 'Organic molecular structure', Willard Grand, Boston (1975), p.528.

56. G. Sosnovskey, Y.I. Yeh and G. Karas, Z. Naturforsch, 28C, 781 (1973).

57. H. Dugas and C. Penney, 'Bio-organic chemistry', Springer-Verlag, New York (1981).

58. R.J.P. Williams, Chemistry in Britain, 1009 (1983).

59. H.D. Gibb's, J. Biol. Chem., 72, 649 (1927).

60. D.R. Armstrong, C. Cameron, D.C. Nonhebel and P.G. Perkins, J. Chem. Soc. Perk. Trans.II, 581 (1983).

61. J.M. Melson and C.R. Dawson, Adv. in Enzymology, 4, 99 (1946).

62. W. Brackman and E. Havinga, Rec. Trav. Chim., 74, 937, 1021, 1070, 1100, 1107 (1955).

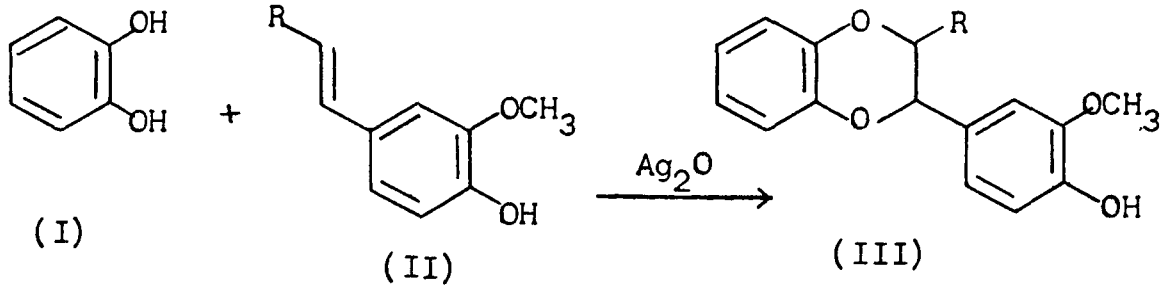
PART II

THEORETICAL

In the recent years, biomimetic synthesis has played an important role in the synthesis of naturally occurring compounds. Studies on non-enzymatic oxygenation as biomimics have contributed not only to the understanding of oxygenase-catalyzed reactions in providing valuable concept for enzymologists, but also to synthetic organic chemists in providing useful synthetic methods.

According to Breslow[1], 'Biomimetic Chemistry is the branch of organic chemistry which attempts to imitate natural reactions and enzymatic processes as a way to improve the power of organic chemistry'. Thus, 'Biomimetic Syntheses' need not be performed under the exact conditions of biosynthesis. Simple and effective laboratory syntheses of complicated natural products, such as alkaloids[2a], lignins[2b] etc. can often be developed by following the biosynthetic pattern.

Oxidation of equimolar amounts of catechol(I) and isoeugenol (IIa) or coniferyl alcohol (IIb) with silver (II) oxide, in benzene containing methanol or acetone, has been reported to give 6-(or 7-) substituted 2,3-trans-benzodioxans (III) via a free radical pathway.

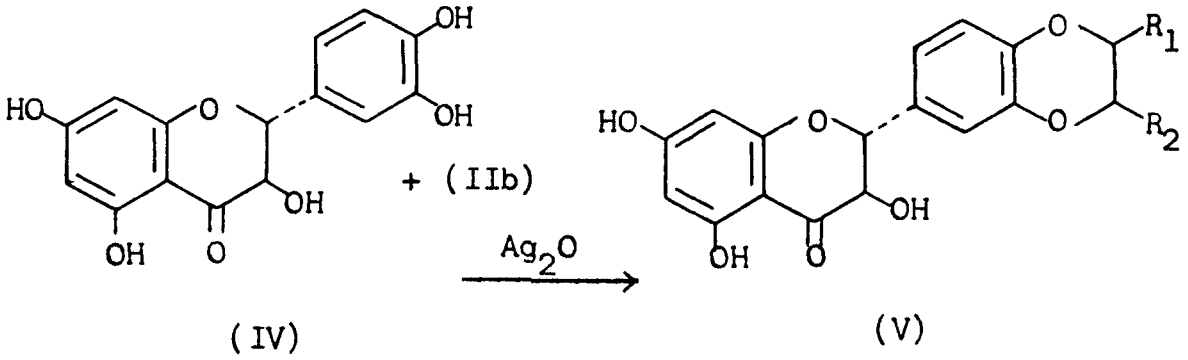


(I) (II) (III)

(a) R= CH_3

(b) R= CH_2OH

Merlini and Zanarotti[2b] have achieved a one step biomimetic synthesis of natural silybin in an analogous reaction. Thus, reaction of equimolar amounts of dihydroquercetin (IV) and coniferyl alcohol (IIb), under almost identical conditions, gave a mixture of two product. The major product was silybin (Va), while isosilybin (Vb) was obtained as the minor product.



(IV) (V)

(a) R_1= CH_2OH

R_2= 3-(OCH_3)-4-(OH)-C_6H_3

(b) R_1= 3-(OCH_3)-4-(OH)-C_6H_3

R_2= CH_2OH

In common with studies of natural products of all kinds, flavonoid chemistry has emerged from the undirected search of new compounds, and the establishment of their structures by conventional means. Substantiation and confirmation of the structures of flavonoid compounds by total synthesis has continued to develope.

The flavonoids, an important group of naturally occurring compounds, are generally polyphenolics possessing 15 carbon atoms skeleton and are represented as the C_6-C_3-C_6 systems. Among flavonoids, the term assigned to this large class of natural substances, derivatives of 2-phenylchroman occupy an important position.

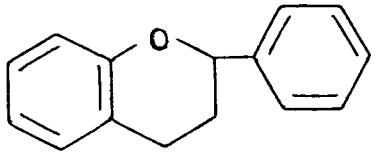
The flavonoids are important to man not only because they contribute to plant colour but also because many members are physiologically active. The importance of flavonoidic compounds in the tanning of leather, the fermentation of tea, the manufacture of cocoa and in the flavour qualities of foodstuff is well established[3a,b]. Certain flavonoids are among the earliest known natural dyestuffs[4a]. They are widely used as antioxidants for fats and oils[5a,b]. Among the physiological activities of flavonoids[3b,4b] include vitamin P activity, diuretic action, treatment of allergy, protection against X-ray and other radiation injuries, cure of frost bite, antibacterial activity, prophylactic action, oestrogenic activity, antitumor effects[6] and anticancer property[7].

The term 'flavonoid' derives from the most common group of compounds, the flavones, where an oxygen bridge between the ortho position of ring A and the benzylic carbon atom adjacent to ring B forms a new γ-pyrone type ring. Such heterocycles, at different oxidation levels, are present in most plants. The flavane corresponds to the lowest oxidation level of ring C, and is taken as the parent structure for the rational nomenclature of this group of compounds.

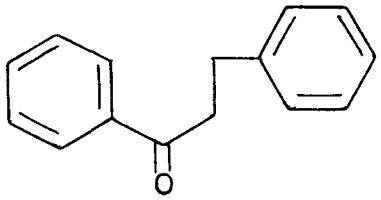
An oxygen bridge involving the central carbon atom of the C_3-chain occurs in a rather limited number of cases, where the resulting heterocycle is of the benzofuran type. The aurones belong to this structural group. The oxygen bridge is absent in chalcones and dihydrochalcones. Principal structural groups of natural flavonoids are shown in Fig.1. The oxidation levels concern the three central carbon atoms: [+1O or -2H]= +1 oxidation unit.

Besidesthe carbon atom link, the flavonoids also have typical oxygenation pattern in their benzene rings . Ring A generally has three alternate oxygens at position 2',4' and 6' in the open formula or, in other words ring A generally derives from phloroglucinol. Compounds having more or less oxygens in their A ring are very seldom encountered. The ring A can be occasionally alkylated with methyl groups, prenyl or prenyl derived units or with glycosides. In contrast, ring B has, in most cases, a para-oxygen substituent, or two oxygens, para- and meta- with respect

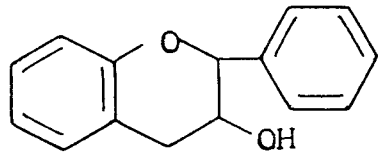
Oxidation level

1. 

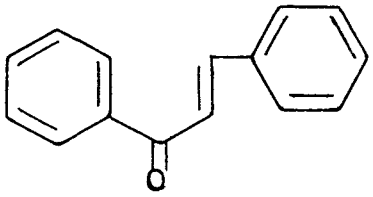
Flavan

2. 

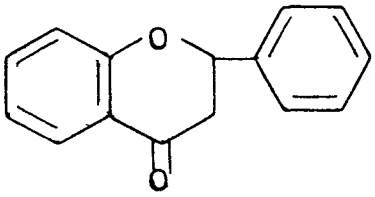
Dihydrochalcone



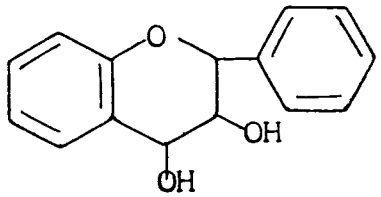
Flavan-3-ol (catechin)

3. 

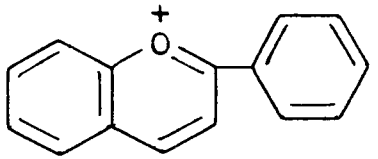
Chalcone



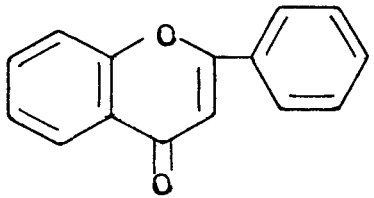
Flavanone



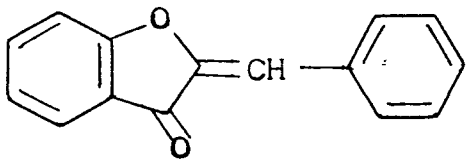
Flavan-3,4-diol



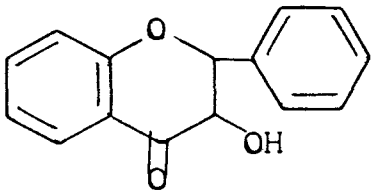
Flavylium salt

4. 

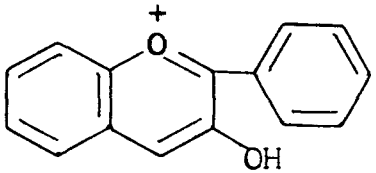
Flavone



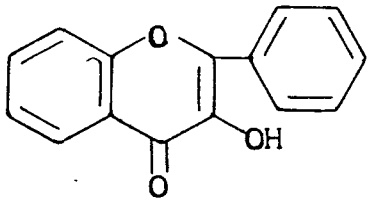
Aurone



Flavanonol



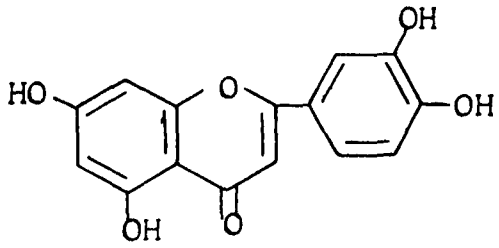
Anthocyanidin

5. 

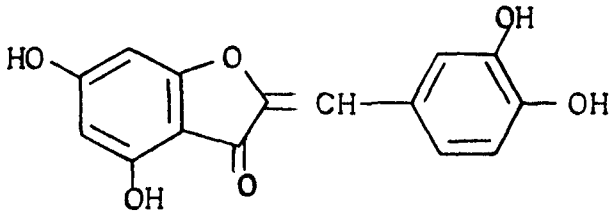
Flavonol

Fig. 1

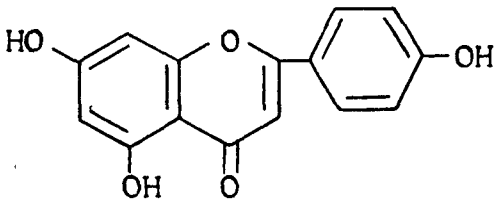
to propane chain. Compounds with non-oxygenated B ring or with one ortho-oxygen function are very rarely found. Compounds bearing three oxygens, one para- and two meta- are less frequent. Typical oxygenation pattern in flavonoid is shown in Fig.2 and Fig.3 shows substitution pattern of the rings A and B in some less common flavonoids.



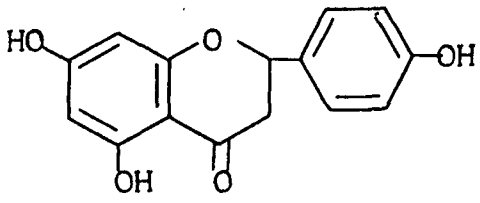
Luteolin



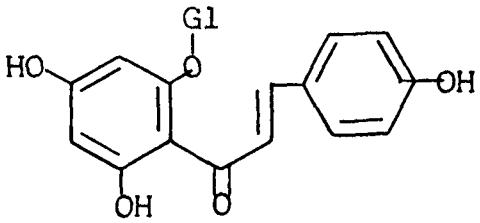
Aureusidin



Apigenin

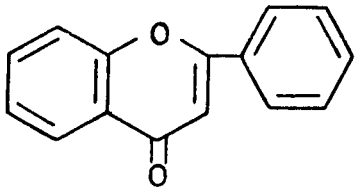


Naringenin

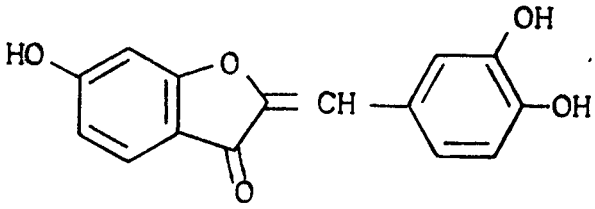


Isosalipurposide

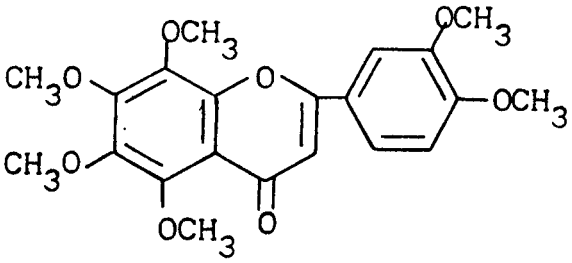
Fig. 2



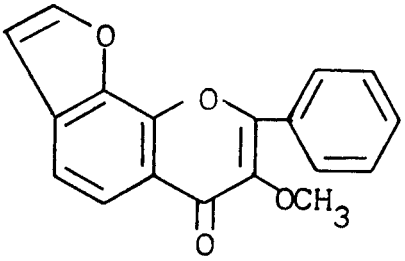
Flavone



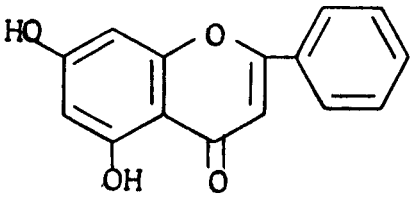
Sulfuretin



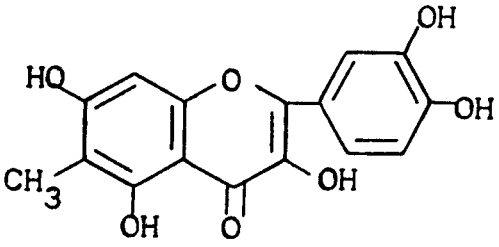
Nobiletin



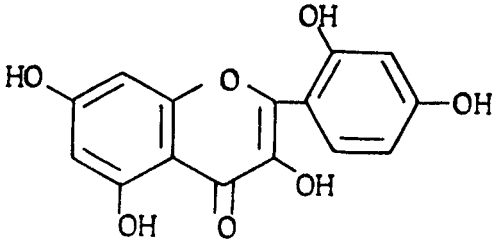
Karanjin



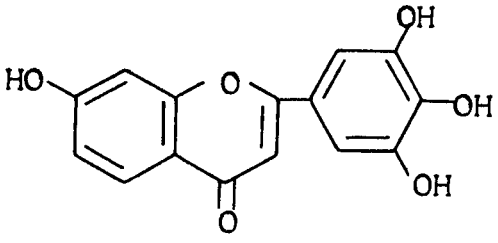
Pinocembrin



Pinoquercetin



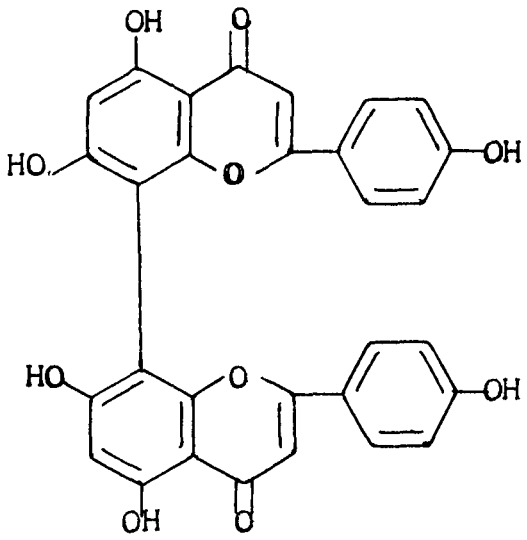
Morin



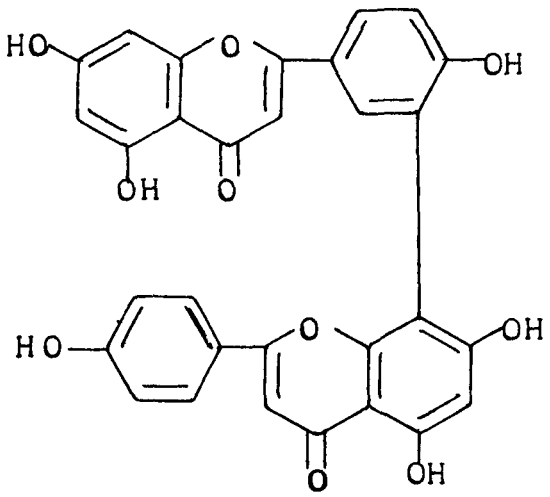
Robinetin

Fig. 3

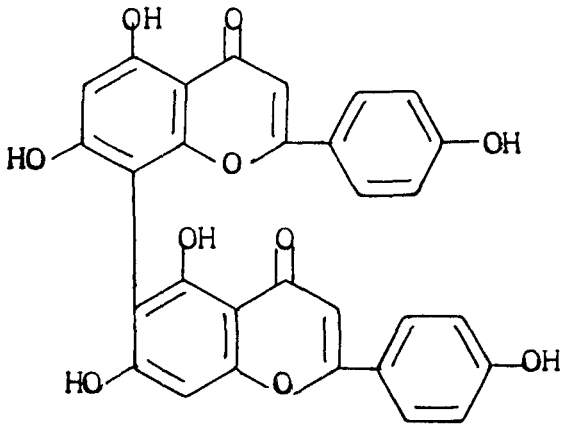
A recent addition to the flavonoid class is 'biflavonoids'. Biflavonoids, which are generally derived from two apigenin or two naringenin or naringenin-apigenin units, have mostly been isolated from gymnosperms. Depending upon the nature and position of the linkage of the constituent monomeric units, all the C-C and C-O-C linked biflavonoids, known to date, are classified into various families[8a]. Representatives of few biflavone families, depending on the position of the linkage of two flavone units, are shown in the Fig.4.



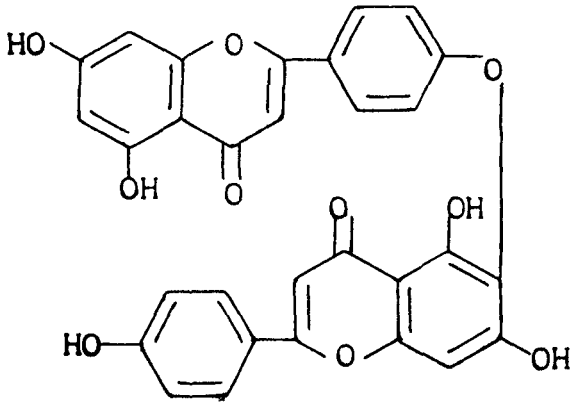
Cupressuflavone



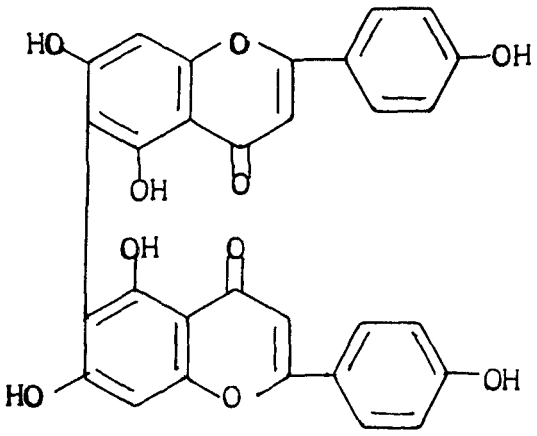
Amentoflavone



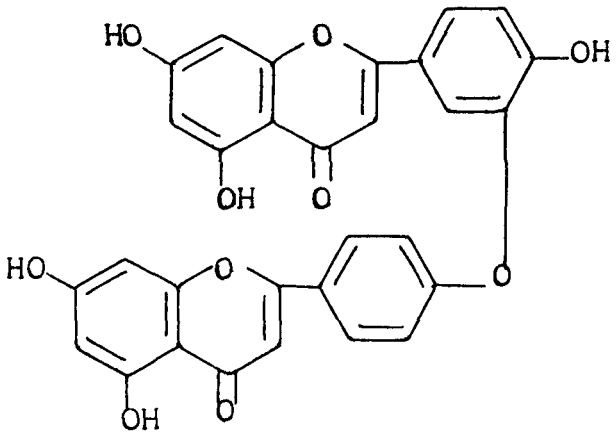
Agathisflavone



Hinokiflavone



Succedaneaflavone



Ochnaflavone

Fig. 4

STRUCTURAL ELUCIDATION OF FLAVONOIDS

The structural elucidation of flavonoids has been discussed in detail in some recent reviews[9] and monographs[8,10]. However, some of the techniques frequently used by us and included in the discussion of this thesis need mention here.

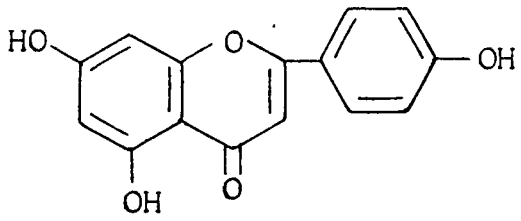
NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

The application of the NMR spectroscopy proved to be the most powerful tool in the structure determination of flavonoids. The valuable contribution in this field has been made by Batterham[11], Mabry[12], Massicot[13], Clark-Lewis[14], Kawano[15] and Pelter and Rahman[16]. Early work on the PMR spectroscopy of flavonoids was hindered by lack of their solubility in $CDCl_3$ and CCl_4. Progress was made following the introduction of Me_2SO-d_6[17], but the most significant advance arose from the conversion of flavonoids into their more soluble trimethylsilyl ethers[18].

The chemical shifts of the protons of rings A and B prove to be independent of each other, but are affected by the nature of ring C[17]. The peaks arising from ring A in most flavonoids occur upfield from other peaks and can readily be recognized.

The most commonly occurring hydroxylation pattern in natural flavonoids is 5,7,4'-trisubstituted system (VI) in which owing to the symmetrical substitution, ring B protons appear as

superimposed doublets (J=9 Hz) corresponding to an A_2B_2 system and ring A protons as AB doublets (J=2.5 Hz). In other cases, however, the interpretation is not so simple owing to the superimposition of signals and appearance of complex multiplicities of protons of an ABX or ABC system.



(VI)

Considerable variations are generally found for the chemical shifts of the ring C protons among various flavonoid classes[10]. For example, the C-3 proton in flavones gives a sharp singlet near ∂ 6.3, the C-2 proton in isoflavones is normally observed at about ∂ 7.7, while the C-2 proton in flavanones is split by C-3 protons into a doublet of doublet (J_{cis}=5 Hz, J_{trans}=11 Hz) and occurs at about ∂ 5.2. The signals for the two C-3 protons appear as a pair of quartets ($J_{H_{3a-3b}}$=17 Hz) near ∂ 2.7-3.0. However, they often appear as two doublets since two signals of each quartet are of low intensity. The C-2 proton in flavanonols appears near ∂ 4.9 as a doublet (J=11 Hz) coupled to the C-3 proton which comes at about ∂ 4.2 as doublet.

Solvent induced shift has been used for assigning the position of methoxyls in methoxyflavones. By measuring the NMR spectra first in $CDCl_3$ and then in C_6D_6, Wilson et al.[19] found that the size of the benzene induced shift (Δ) of certain methoxyl signals was to some extent indicative of the position of the methoxy group in the flavone nucleus.

A more recent innovation in this field is that of lanthanide induced shift[15]. The technique is extremely helpful in establishing the internuclear linkage of biflavonoids and also for the distinction of A and B ring methoxy signals.

MASS SPECTROMETRY

Electron impact mass spectrometry serves as a valuable tool in the structure determination of flavonoids, especially when only very small quantities of the compounds are available. It has been applied successfully to all kinds of flavonoids.

Most flavonoid aglycones yield intense peaks for the molecular ion ($M^{+\cdot}$). In addition, peaks for $(M-H)^+$ and, when methoxylated, $(M-CH_3)^+$ are usually the major peaks. The most useful fragmentations in terms of flavonoid identification are those which involve cleavage of intact A- and B-ring fragments[8b].

Two common fragmentation patterns of flavonoids are, an exception being chalcones which undergo direct fission on each

side of carbonyl group, retro-Diels-Alder cleavage, pathway I and pathway II. Pathway I (RDA) process affords two different ions, the ratio of the two being indicative of the charge distribution within the parent ion. In contrast, pathway II yields predominantly a single charged species. These two fragmentation processes are competitive and the combined intensities of the pathway II ion and ion derived from this ion are approximately inversely proportional to those of pathway I fragments and the series of ions derived from them.

The flavones were among the first flavonoids to be analyzed by mass spectrometry[20,21]. Although molecular ion, $M^{+\cdot}$, is the base peak for most of the flavones, the fragment $(M-CO)^{+\cdot}$ and pathway I fragments $A_1^{+\cdot}$ and $B_1^{+\cdot}$ are usually prominent. An ion $(M-1)^+$ is often found in the mass spectra of flavones, its origin, however, is obscure. Pathway II fragment, B_2^+, though usually found is not much intense. The diagnostic fragmentation pattern for flavones is illustrated in Fig.5 taking apigenin (VI) as an example.

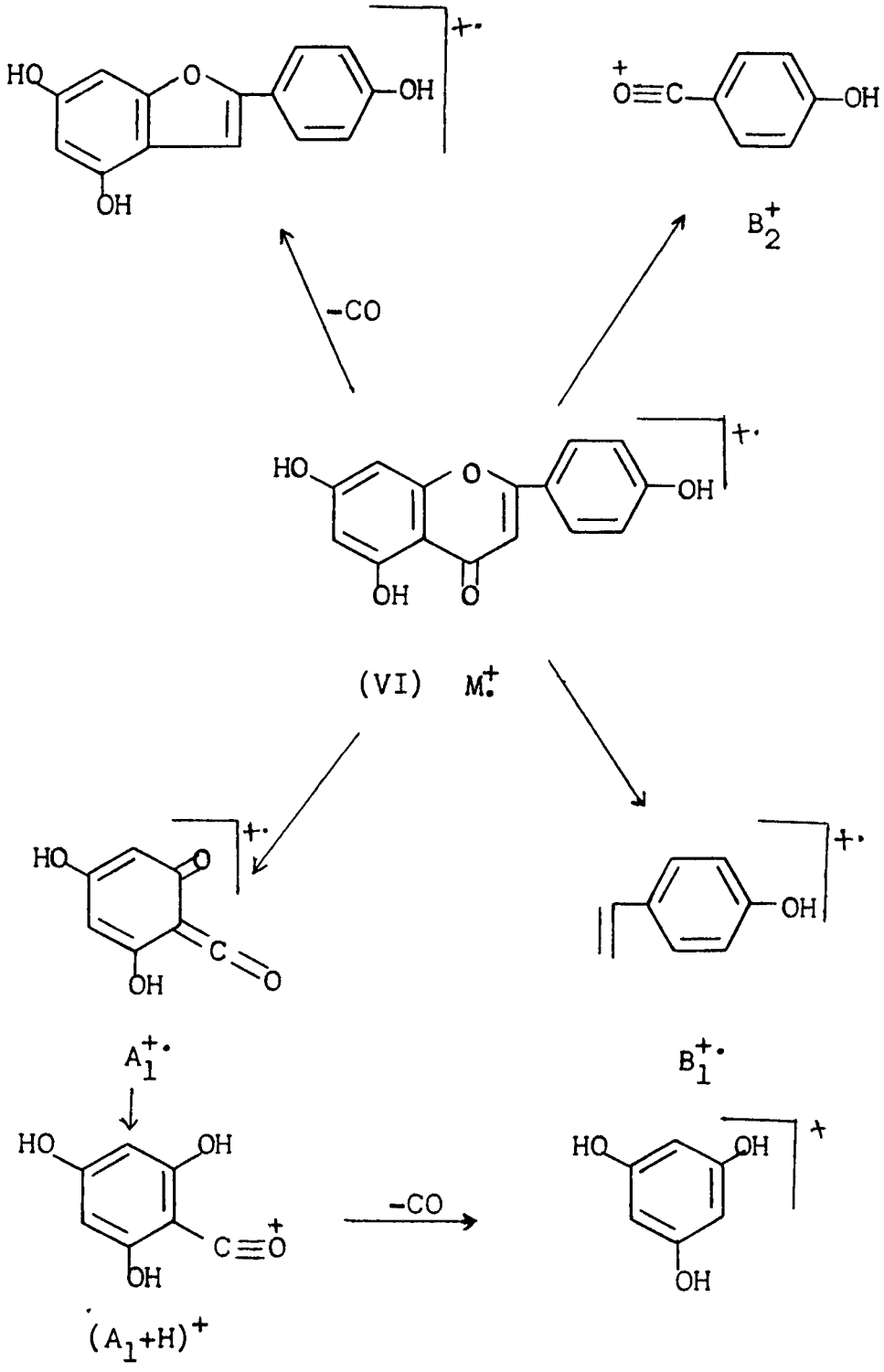
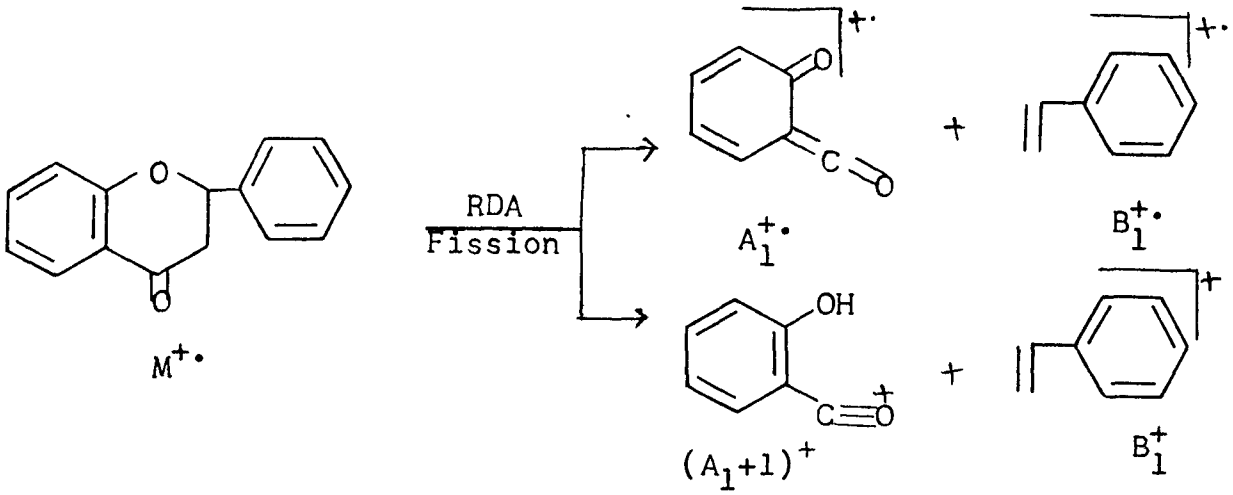
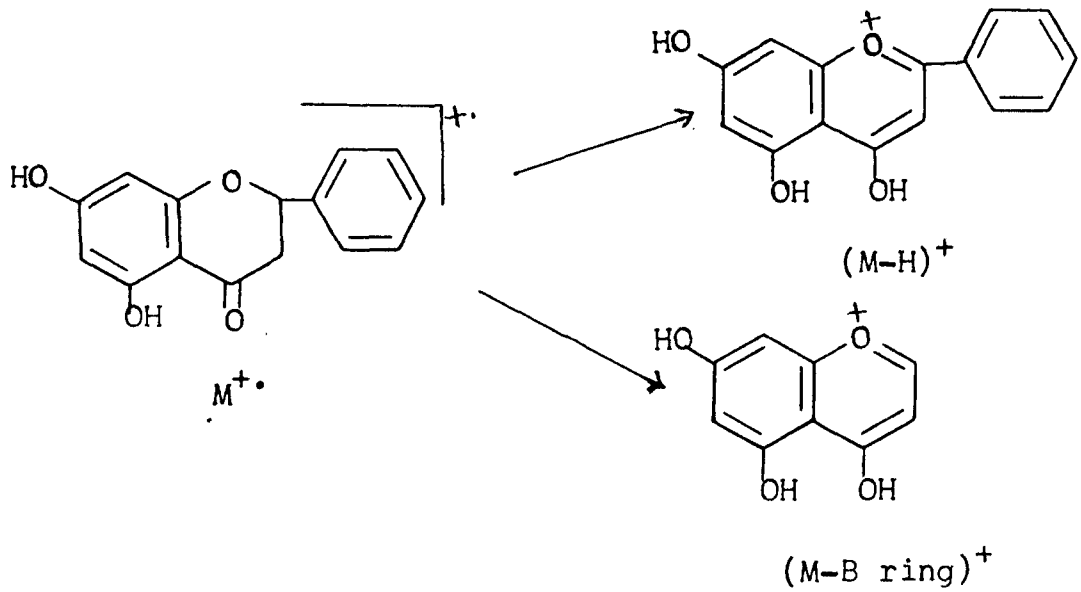

HO
O
OH
OH
+·
O≡C
OH
B_2^+
-CO
HO
O
OH
OH
O
+·
(VI) $M^{+\cdot}$
HO
O
C
O
OH
+·
OH
+·
$A_1^{+\cdot}$
$B_1^{+\cdot}$
HO
OH
C≡O
OH
-CO
HO
OH
+
OH
$(A_1+H)^+$

Fig. 5

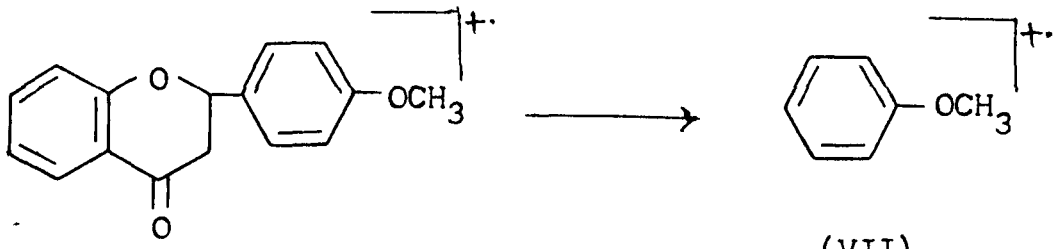
In the case of flavonoids with reduced heterocyclic ring, typical fragmentation by RDA process yields ion which correspond to the same $A_1^{+\cdot}$ and $(A_1+1)^+$ ions observed for flavones; however the B-ring ion contains an ethylene group[22,23].



Another diagnostic fragmentation, that helps in structure determination of flavanones, is the loss of either a hydrogen or an aryl radical to produce $(M-H)^+$ and $[M-(B\text{-ring})]^+$ ions.

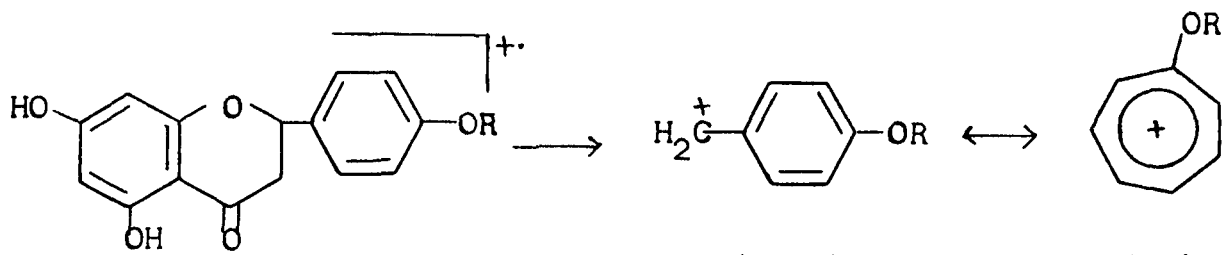


A moderately intense B-ring ion (VII) is found in the case of 4'-methoxyflavanones which is formed by the fission of the B-ring from the molecular ion accompanied by a hydrogen transfer.



$M^{+\cdot}$ (VII)

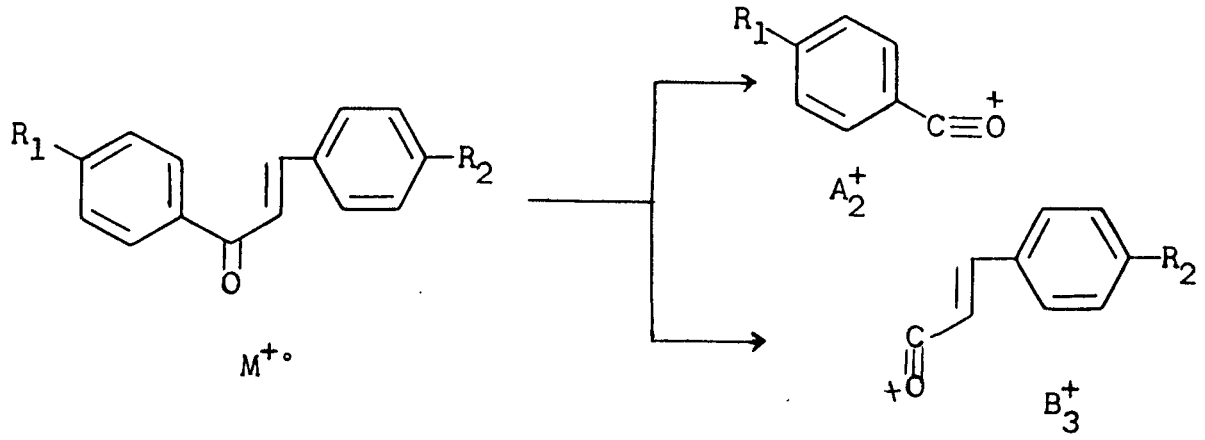
The presence of a hydroxyl or a methoxyl group at C-4' facilitates, by the enhanced resonance stabilization of the molecular ion, the formation of p-hydroxybenzyl or p-methoxybenzyl ion (VIII) respectively. The prominence of this ion may be associated with its rearrangement to a tropolium structure (IX).



$M^{+\cdot}$ (VIII) (IX)

R= H, CH_3

Chalcones give strong ions for $M^{+\bullet}$, $(M-H)^+$ and $(M-CH_3)^+$ (for methoxychalcones). However, most diagnostic fragments result by the fission on either side of the carbonyl group. The relative intensities of these ions, designated as A_2^+ and B_3^+, and of those derived from them, depend upon the substitution pattern of the chalcone[23,24].



It has been established, in the case of 2'-hydroxy-chalcones, that an equilibrium exists between chalcone and flavanone and the ions derived by fragmentation of both the chalcone and its corresponding flavanone are found in the mass spectrum. In some cases, however, the cleavage of the chalcone adjacent to the carbonyl group is much faster than the isomerization to flavanone and thus the spectrum of the chalcone predominates. It has been emphasized that, in most cases, it is difficult to determine with certainty from the mass spectral data whether chalcone or flavanone was originally present.

Mass spectrometry has been very useful in the structure elucidation of biflavonoids. Biflavonoids have mostly been studied as their permethylated derivatives[9]. In general, two flavonoid units of a C-C linked biflavonoid fragment by some of the pathways which are well defined for the corresponding monoflavonoids. Some A- and B-ring fragmentsare exactly the same as those observed for the monoflavonoids, while other are typical A- and B-ring fragments except that they have an intact flavonoid unit attached to them[25]. The C-O-C linked biflavonoids undergo fission on both the sides of the ether linkage to yield ions which undergo further fragmentation. Doubly charged ions are usually present.

BIOGENESIS

Chemical speculations on the mode of formation of the carbon skeleton of this large class of natural product stimulated the interest in the biosynthesis of flavonoids. Although the origin of the carbon atoms of flavonoid is well known[26-28], the actual compounds that condense to yield the C_{15}-skeleton and the sequence of changes which results in the formation of a relatively diverse group of compounds, based on variation in the oxidation level of the C_3-portion of the molecules, are less well understood.

Basically ring A is formed by head-to-tail condensation of three acetate units while ring B as well as C_3-chain arise from a phenylpropanoid precursor derived from the shikimic acid pathway[29]. The involvement of acetic acid and substituted cinnamic acid has been confirmed through studies with labelled compounds, notably by Grisebach[30] and Geissman[31] (Fig.6).

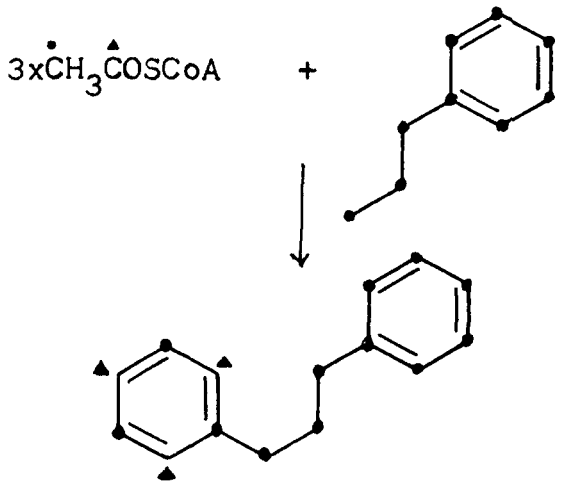


Fig. 6

However, a more detailed knowledge of this reaction and of the chemical nature of the immediate precursors obtained from the enzymic studies support the proposal that CoA ester of malonic acid and cinnamic acid are the substrates of an enzyme-mediated condensation (Fig.7)[32,33]. While no experimental evidence has been obtained, so far, regarding the possible intermediates in the formation of ring A from acetyl CoA, direct evidence for the reaction mechanism formulated in Fig.7 has been obtained from the chemical degradation of the overall product formed from p-coumaroyl CoA and ^{14}C-labelled malonyl CoA with an enzyme preparation from cell suspension cultures of parsley[34].

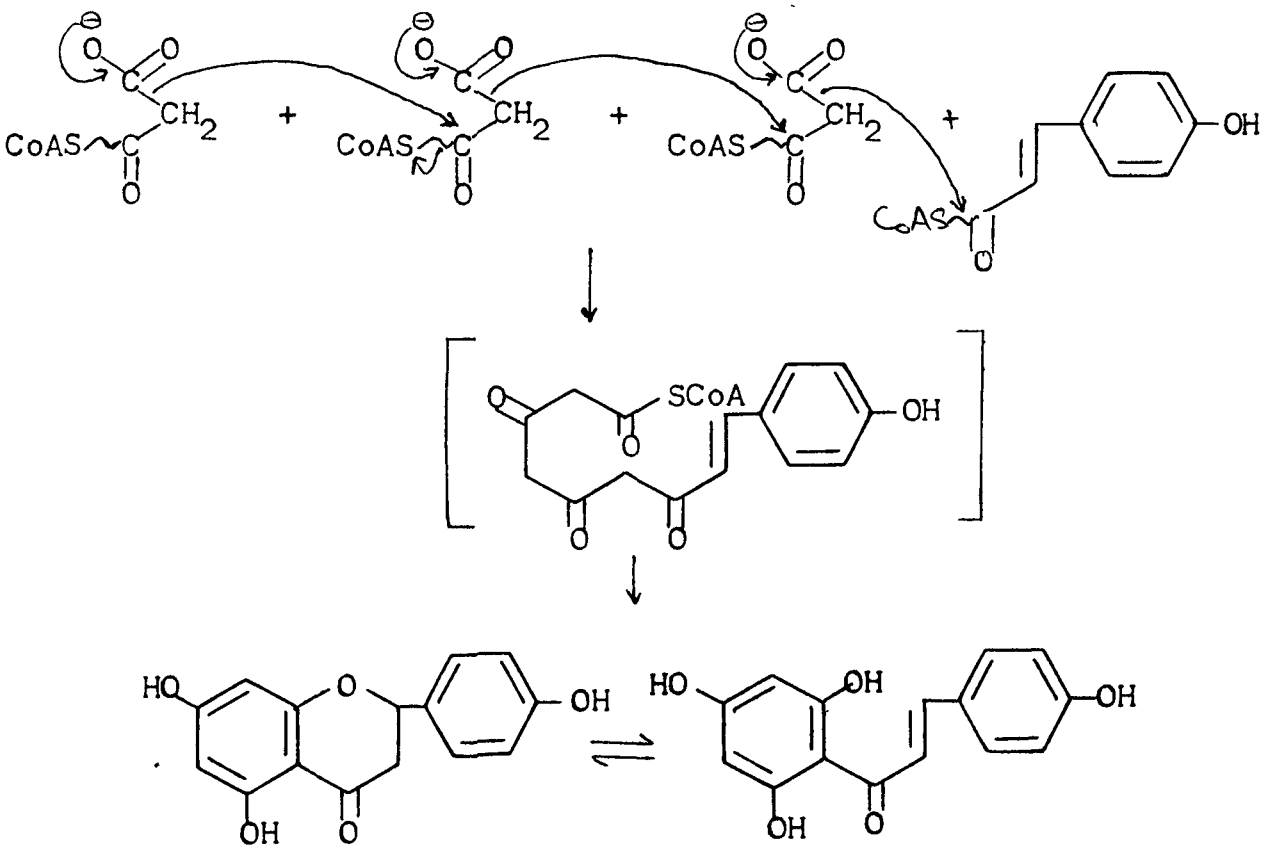


Fig. 7

There are still some doubts as to the actual structure of the phenylpropane unit used by the plants as a starter for the process of polyketide condensation and then ring A. Most chemists now believe that the cinnamic acids (p-coumaric, and more rarely caffeic, ferulic and sinapic acids) are obligatory intermediates in the biosynthesis of most flavonoids.

It has been repeatedly demonstrated, using labelled chalcones[35,36] and flavanones[37,38], that these compounds are the central intermediates from which most, if not all, other flavonoids originate. Conclusive evidence has not, so far, been obtained to answer the question whether chalcones or flavanones are the more direct precursors of the various flavonoids. There is good evidence for the *in vitro*[39] and *in vivo*[40] existence of an equilibrium between chalcones and the corresponding flavanones. The chalcone-flavanone interconversion is catalyzed *in vivo* by an enzyme, chalcone-flavanone isomerase, isolated from various plant sources[8].

The more important naturally occurring flavonoids are at the same or a higher oxidation level than flavanones, and many special hypotheses have been proposed to explain the genesis of each series.

The first oxidative hypothesis for flavonoid biosynthesis was proposed by Grisebach[41], who also made a detailed experimental study into the chemistry and biochemistry of flavonoids. The main

feature of Grisebach's hypothesis was the formation of an epoxide chalcone (X), which could lead to flavonols, aurones, flavones and isoflavones, through plausible chemical mechanisms (Fig.-8).

The weakest point of the epoxide hypothesis is that the natural chalcone epoxides are as yet unknown, α,β-unsaturated ketones reacting slowly or not at all with peracids[42], that although, synthetic 2'-OR chalcone epoxides are known[43], their epoxidation with H_2O_2 requires strongly alkaline conditions which are conditions totally different from those occurring *in vivo*[44,45].

There are alternative oxidation paths, which involve either the enolic form of the flavanone (XI) followed by an attack by the equivalent of $\overset{+}{O}H$ and/or direct oxidation of a flavanone to afford a cation at C-3 (XII) which could be transformed to a flavone, flavanonol or isoflavone[46,47] (Fig.-9). These hypotheses also give satisfactory explanation for the biogenetic correlations amongst the various flavonoids and, specially, for the very frequent presence of an oxygen atom in position C-3. However, the mechanism proposed for the direct oxidation of flavanone to give a flavanone C-3 cation followed by reaction with $\overset{-}{O}H$, and enolization of the flavanone followed by attack by equivalent of $\overset{+}{O}H$ are doubtfully feasible *in vitro*.

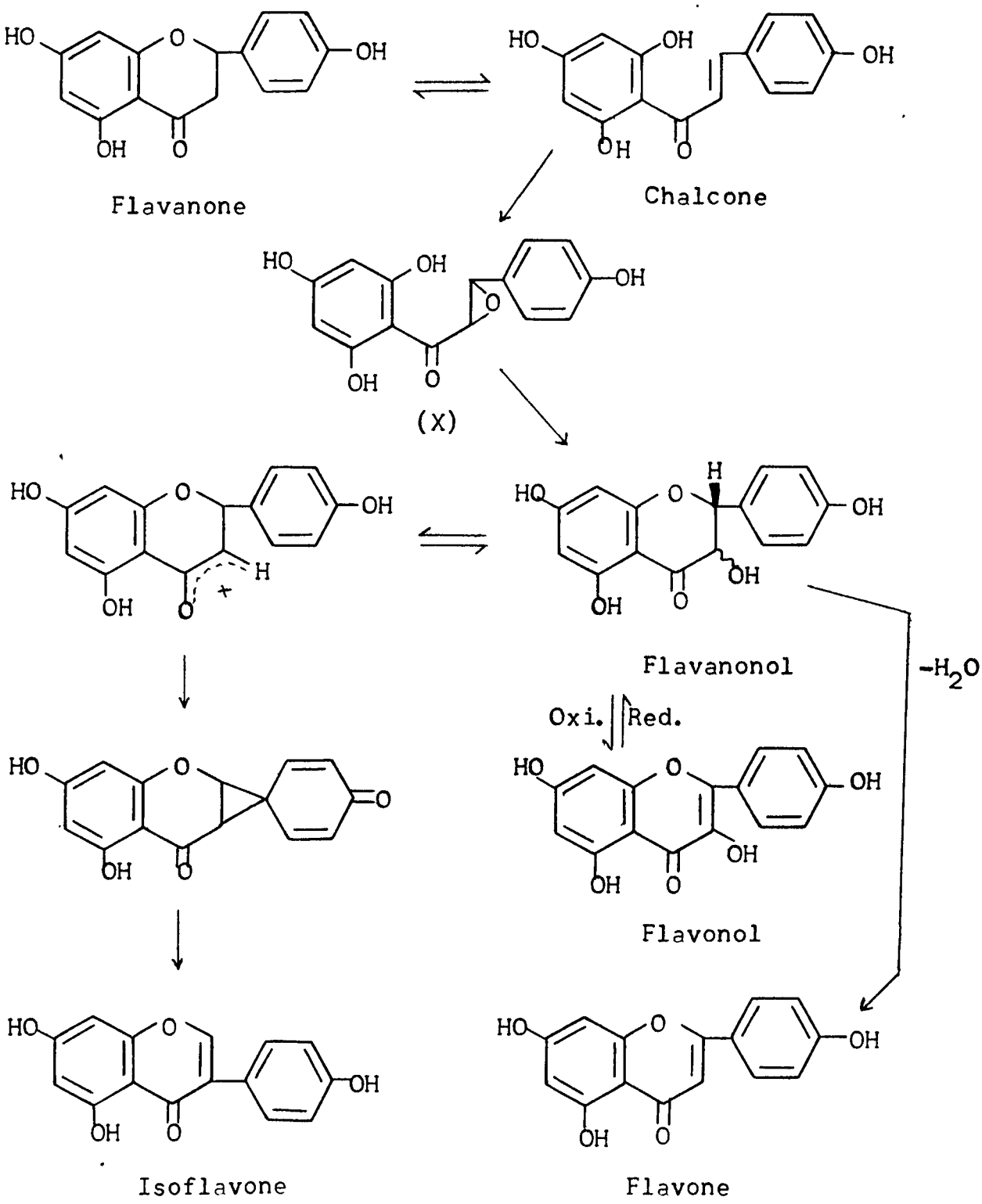

Flavanone
Chalcone
(X)
Flavanonol
Oxi.
Red.
Flavonol
Isoflavone
Flavone
-H2O

Fig. 8

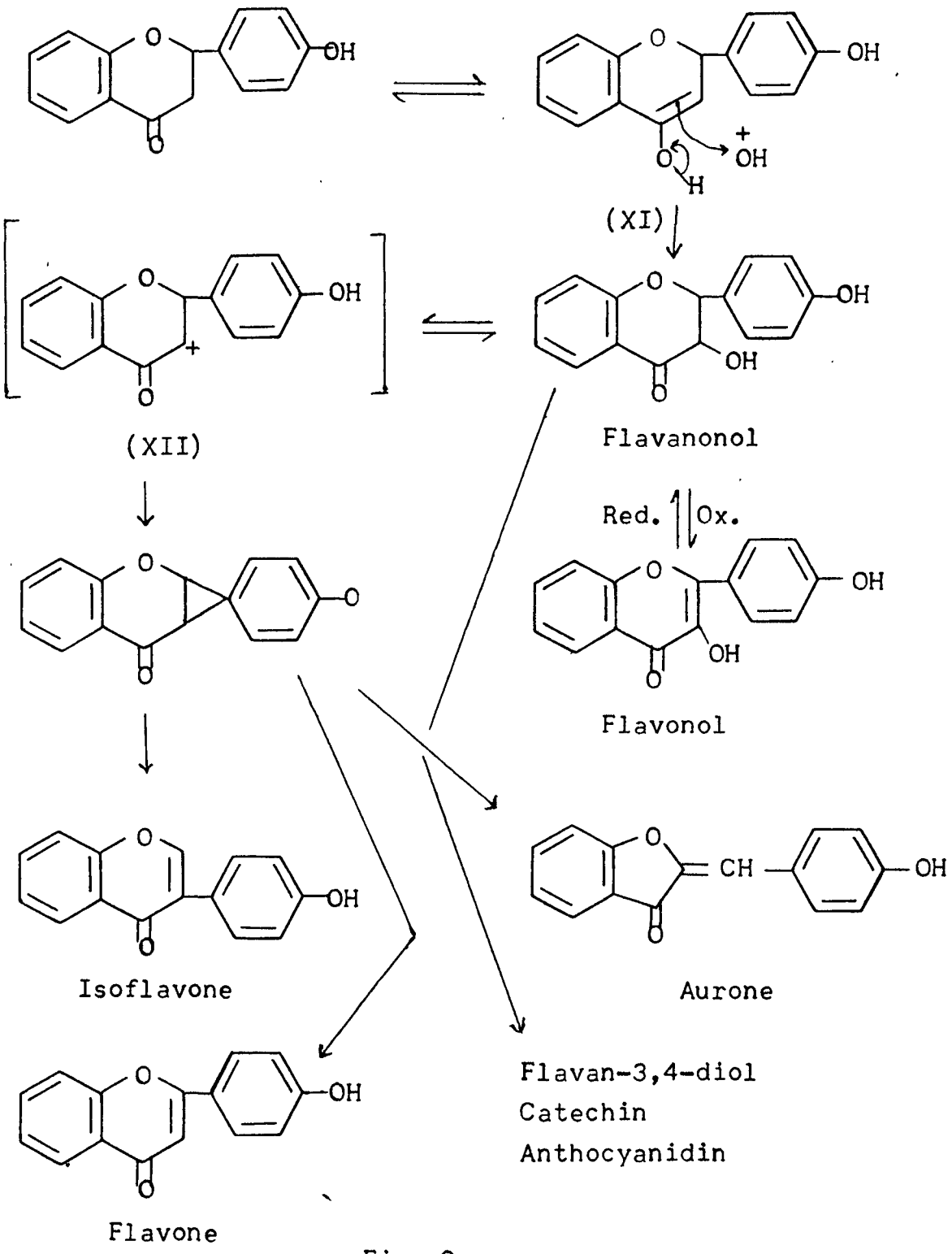
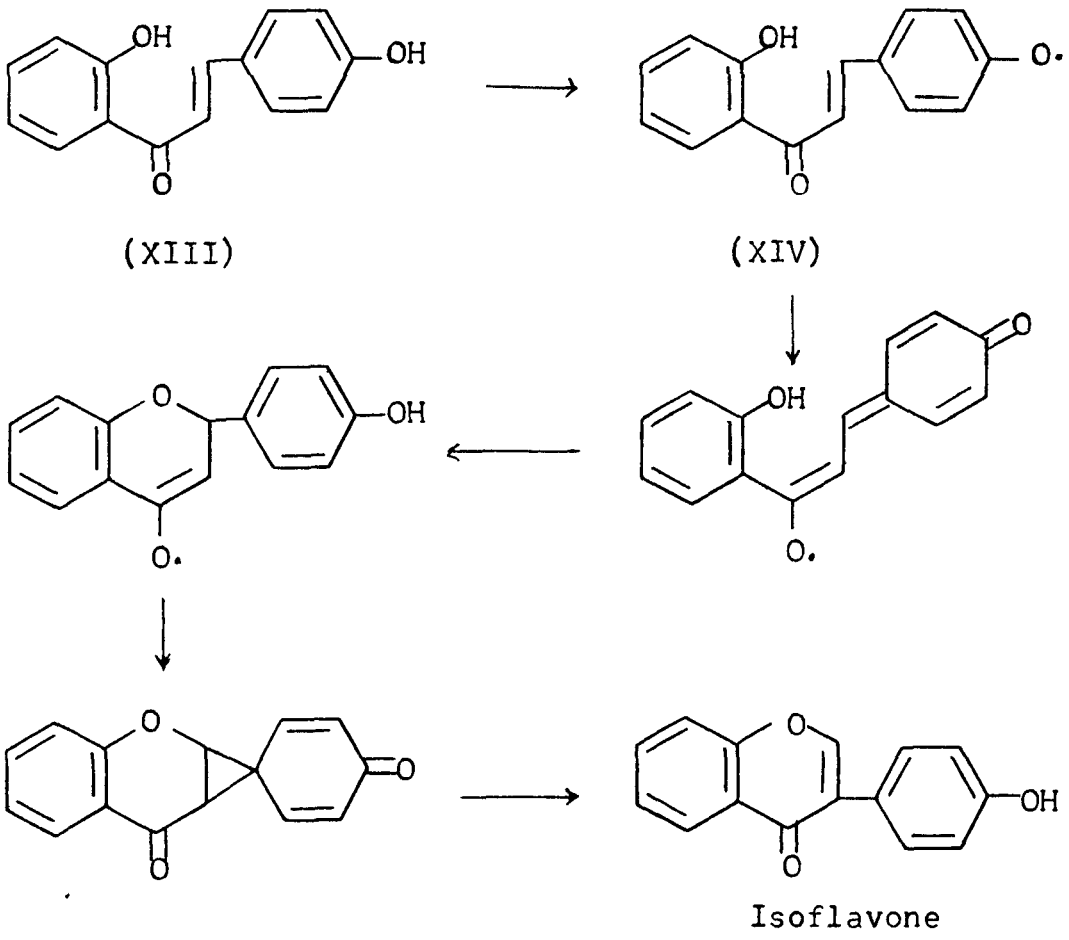

(XI)
(XII)
Flavanonol
Red.
Ox.
Flavonol
Isoflavone
Aurone
Flavan-3,4-diol
Catechin
Anthocyanidin
Flavone

Fig. 9

Pelter[48] made a detailed experimental study into the chemistry of flavonoids and put forward a hypothesis, based on the phenolic oxidation of 4-hydroxychalcones (XIII) which is supported by a large number of in vitro chemical analogies. Pelter suggested that a hydrogen (or hydride) abstraction from the 2- or 4-hydroxyl group generates a radical (or cation) (XIV) which induces cyclization as depicted in Fig.10 to give isoflavone.



Isoflavone

Fig. 10

Formation of flavones and aurones can be explained from the radical (XIVa) depicted in Fig.11. The formation of flavonols can be explained in terms of oxidation of either flavanonols or flavones (Fig.-12).

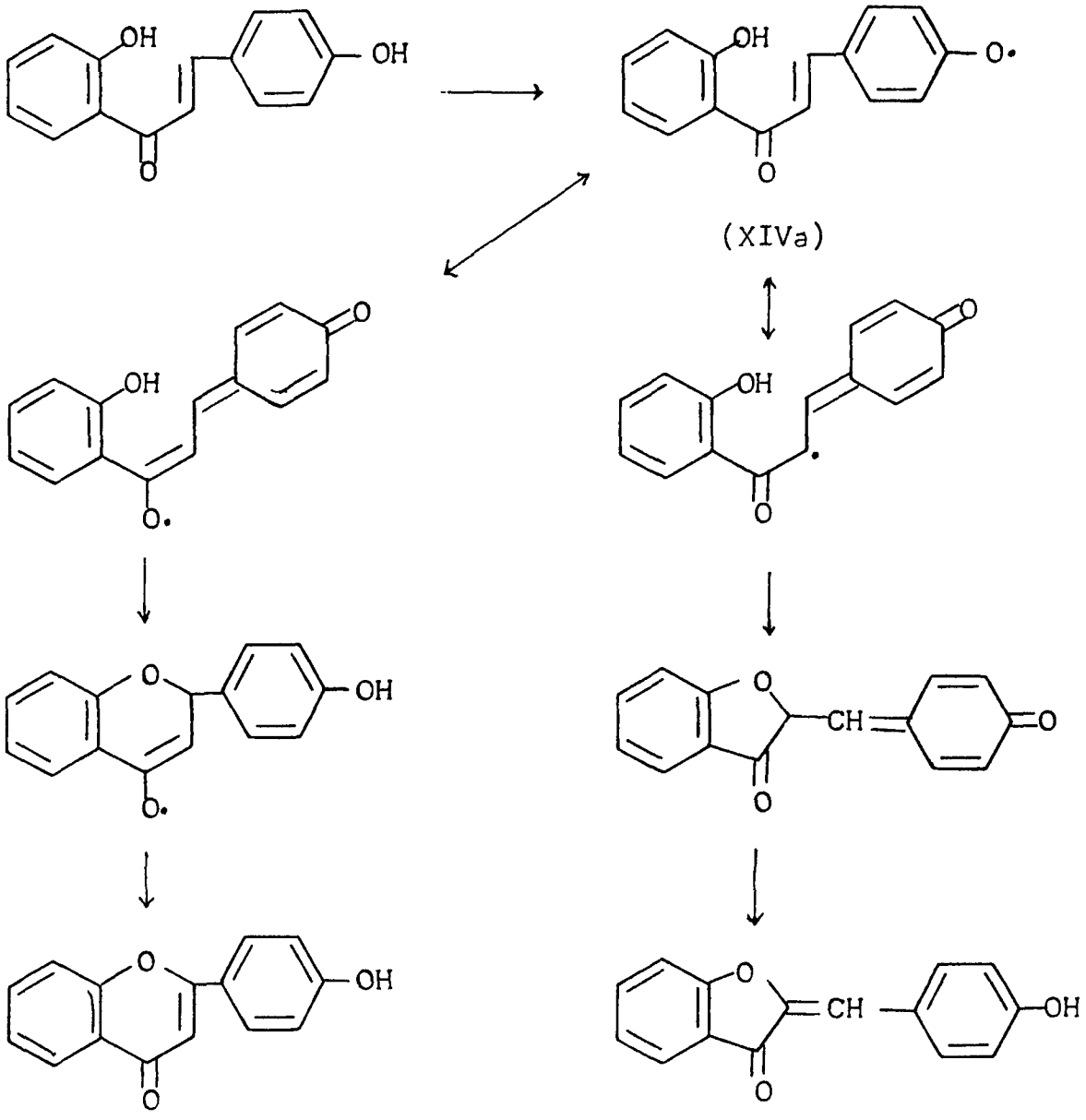


Fig. 11

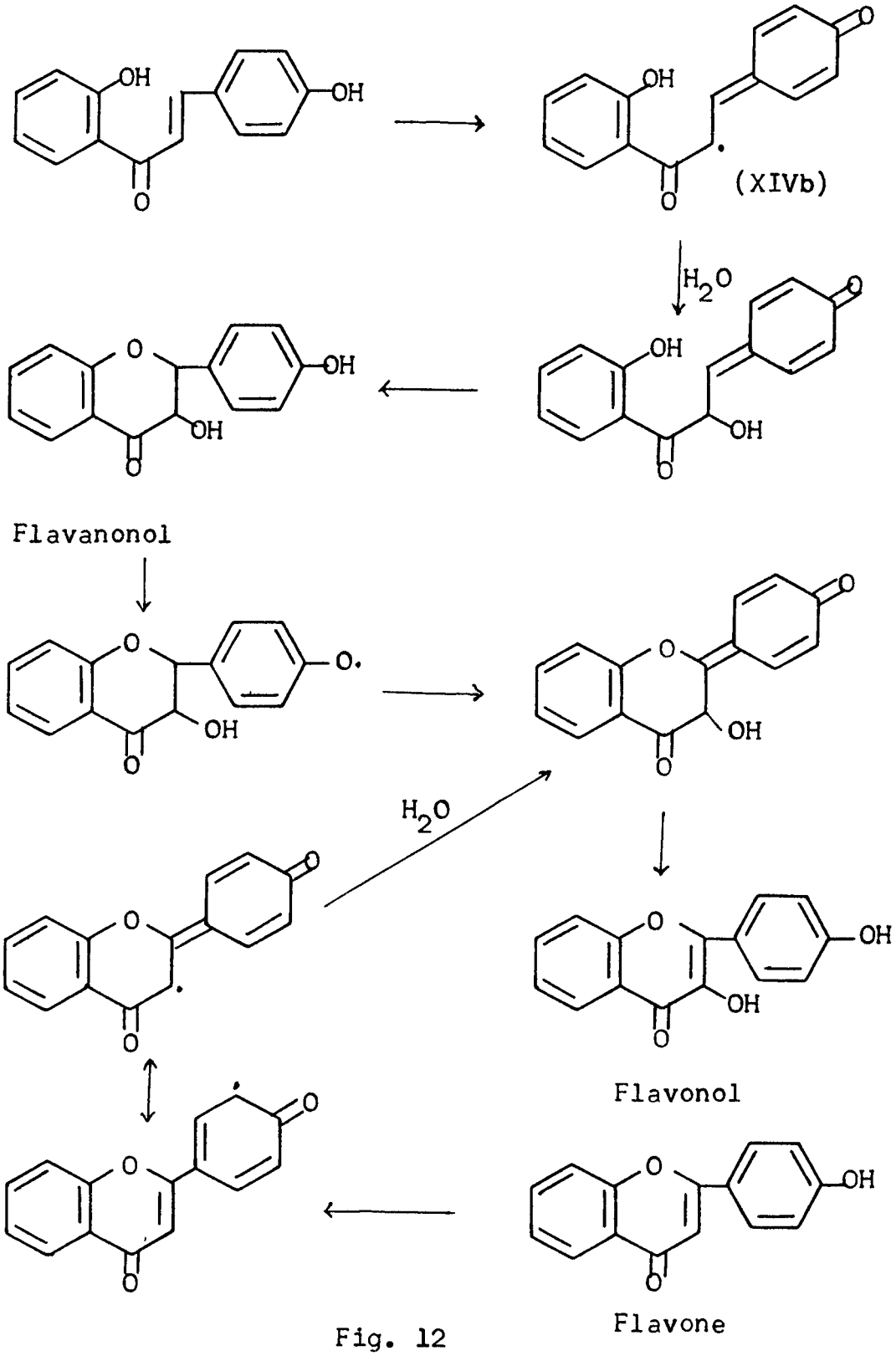
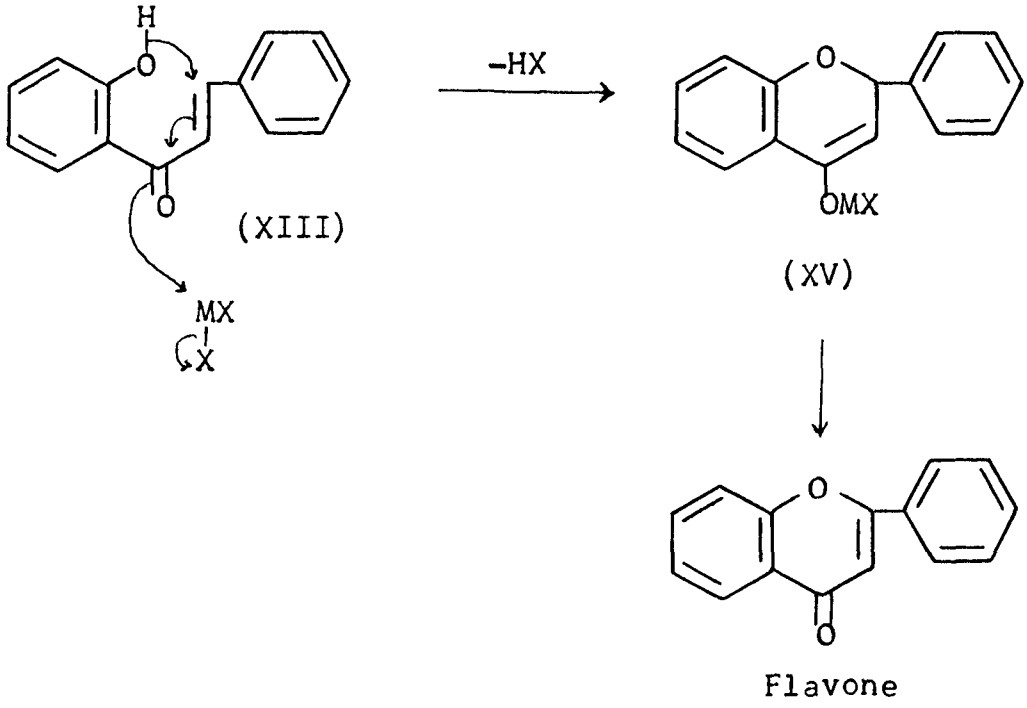

OH
OH
O
OH
O
(XIVb)
H_2O
O
OH
OH
O
O
OH
Flavanonol
O
O.
OH
O
O
OH
H_2O
O
OH
O
O
Flavonol
O
OH
O
Flavone

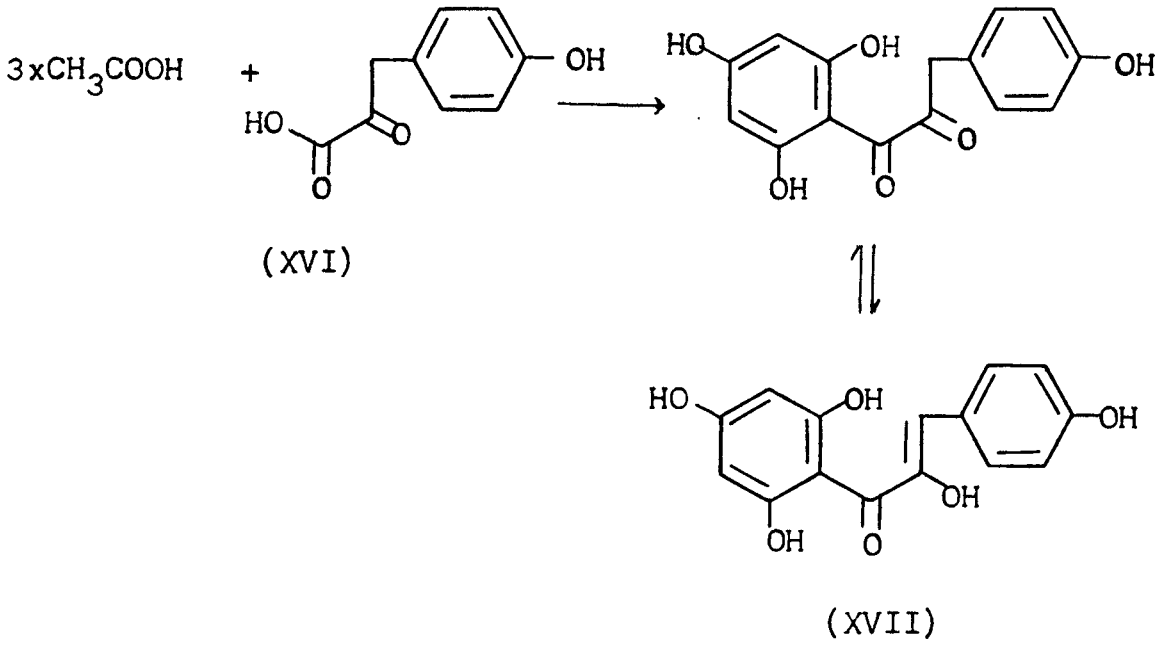
Fig. 12

The production of the flavonoids devoid of a hydroxyl group on the B-ring and above the flavanone oxidation level is not explained by Pelter's hypothesis. Pelter suggested that these compounds are probably produced directly from chalcones as shown in scheme I. Cyclization of the 2'-hydroxychalcone (XIII) is initiated by a metal ion to yield the metal enolate (XV) followed by an oxidative loss of the metal to yield flavone.



Scheme I

Roux and Ferreira[49] have recently proposed another hypothesis for the flavonoids biosynthesis from α-hydroxychalcone (XVII) which probably originate from p-hydroxyphenylpyruvic acid (XVI)[50,51] and malonate (or acetate) units. The Roux theory is supported by the large natural distribution of α-hydroxychalcones[52,53].



(XVI)

(XVII)

The formation of both 2,3-cis- and 2,3-trans-flavanonols can be explained by the cyclization of the enolic form of α-hydroxychalcones (XVII). Subsequent reduction of these flavanonols leads feasibly to 2,3-cis- and 2,3-trans-flavan-3,4-diols and eventually to corresponding flavan-3-ols (Fig.-13). These classes of compounds form flavonols and anthocyanidins by oxidation and elimination reaction, respectively.

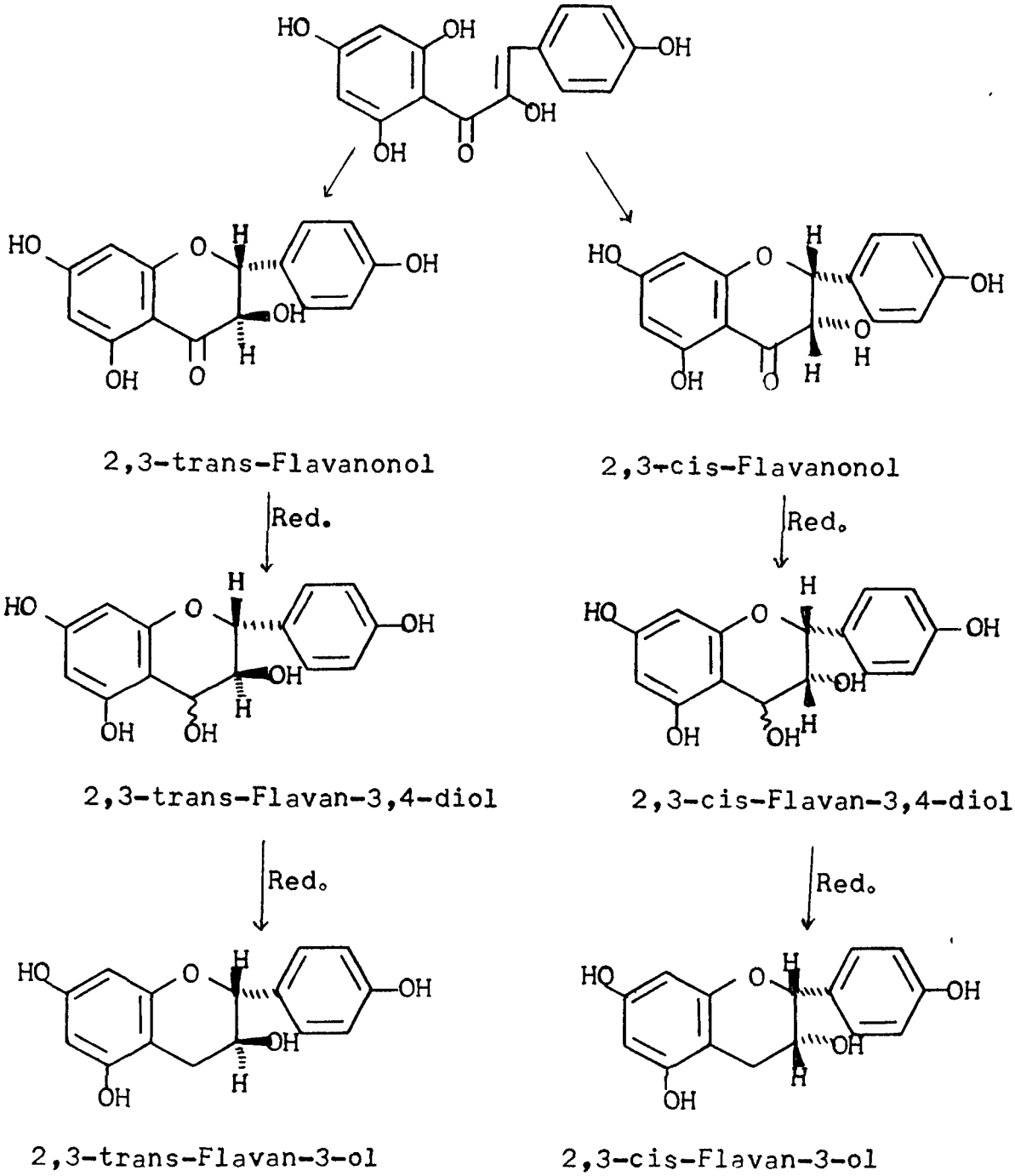
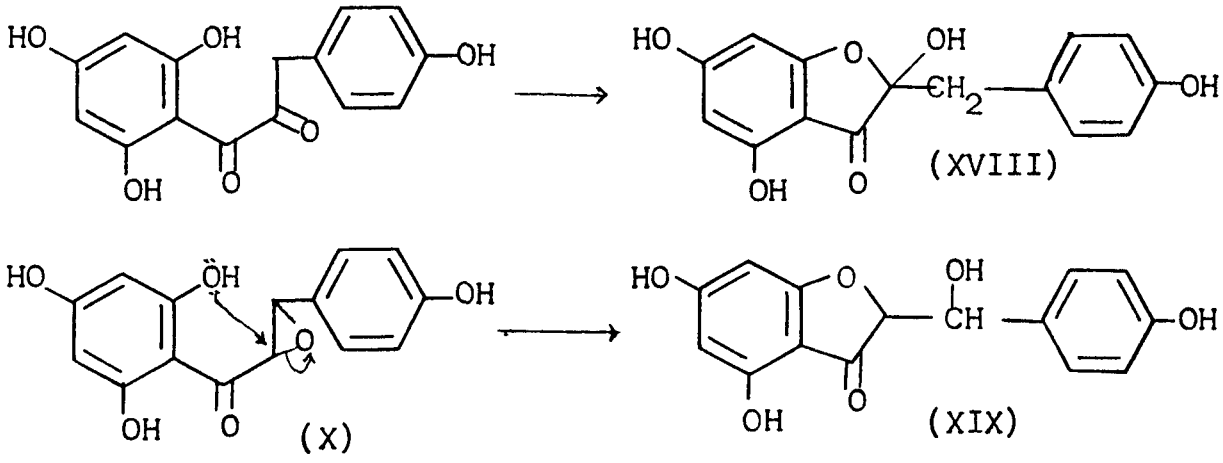

2,3-trans-Flavanonol
2,3-cis-Flavanonol
Red.
Red.
2,3-trans-Flavan-3,4-diol
2,3-cis-Flavan-3,4-diol
Red.
Red.
2,3-trans-Flavan-3-ol
2,3-cis-Flavan-3-ol

Fig. 13

2-Hydroxy-2-benzylcoumaranones (XVIII) may be formed by the alternative method of cyclization to the α-position of the enolic form of the α-hydroxychalcone (XVII) or more likely to the corresponding carbonyl group of the keto-isomer. Such a cyclization requires acid conditions for the enolic ether form[52], while those for the keto form are as yet unestablished. The formation of 2-hydroxy-2-benzylcoumaranones (XVIII) can not be explained by the epoxide induced biosynthesis where the alternative method of cyclization[54] provides (hydroxybenzyl) coumaranone (XIX) and not (XVIII).



Another hypothesis[55] (Fig.-14), postulates a simultaneous phenol oxidation of the two aromatic rings of the chalcone intermediate, followed by an intramolecular coupling, according to a scheme very common in plants. Intermediates such as (XXI) and (XXII) (oxonium salts) should be formed, which could lead to aurone, flavone, flavanonol and isoflavone.

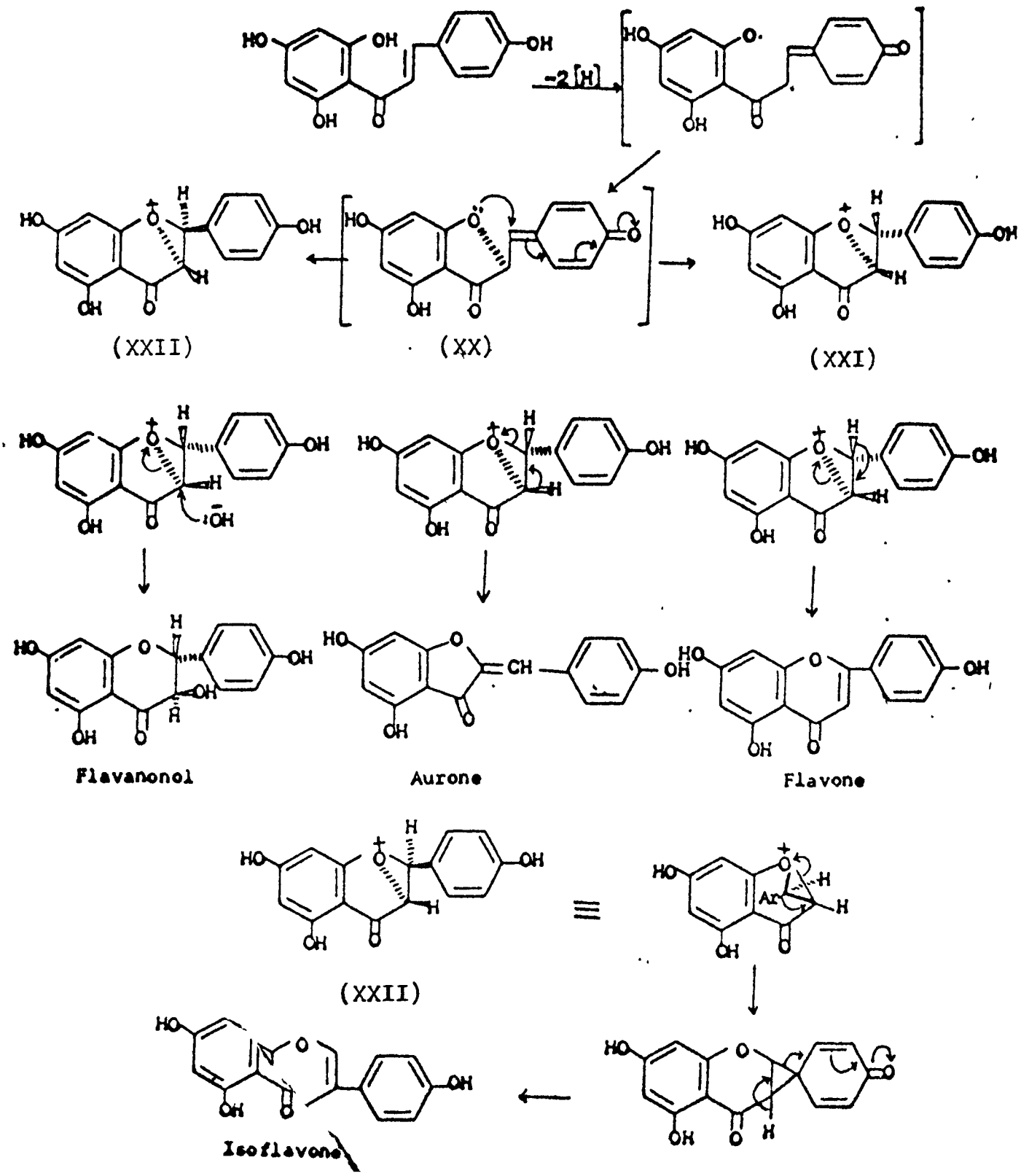
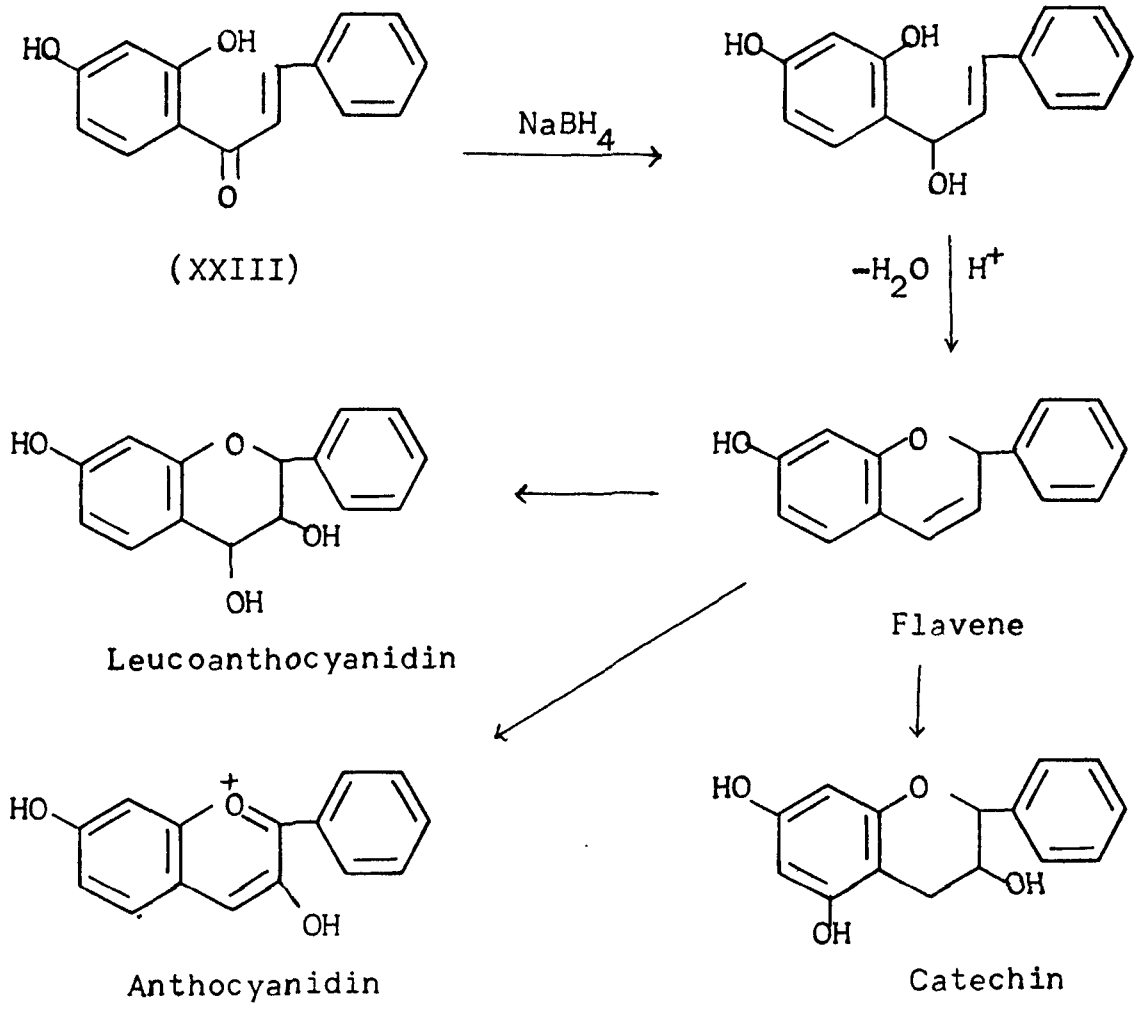


Fig.14

Reduction of flavanonols is assumed in the biogenesis of flavonoid structures in low oxidation level but other possibilities exist. Thus as shown by Clark-Lewis and co-workers[56,57] sodium borohydride reduction of chalcones (XXIII) give flavenes, which can conceiveably also serve as precursors of leucoanthocyanidins, anthocyanidins and catechins[58].



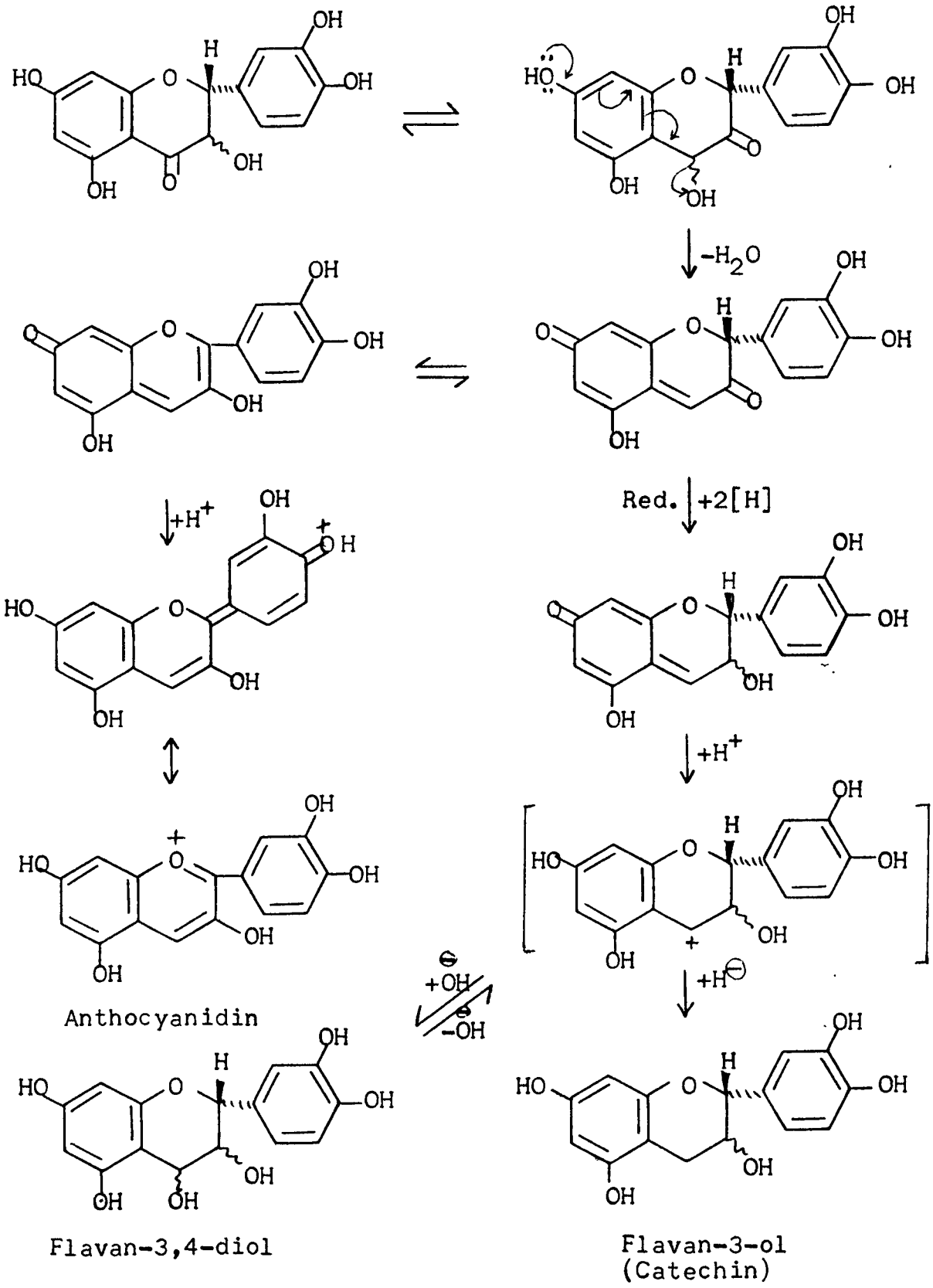
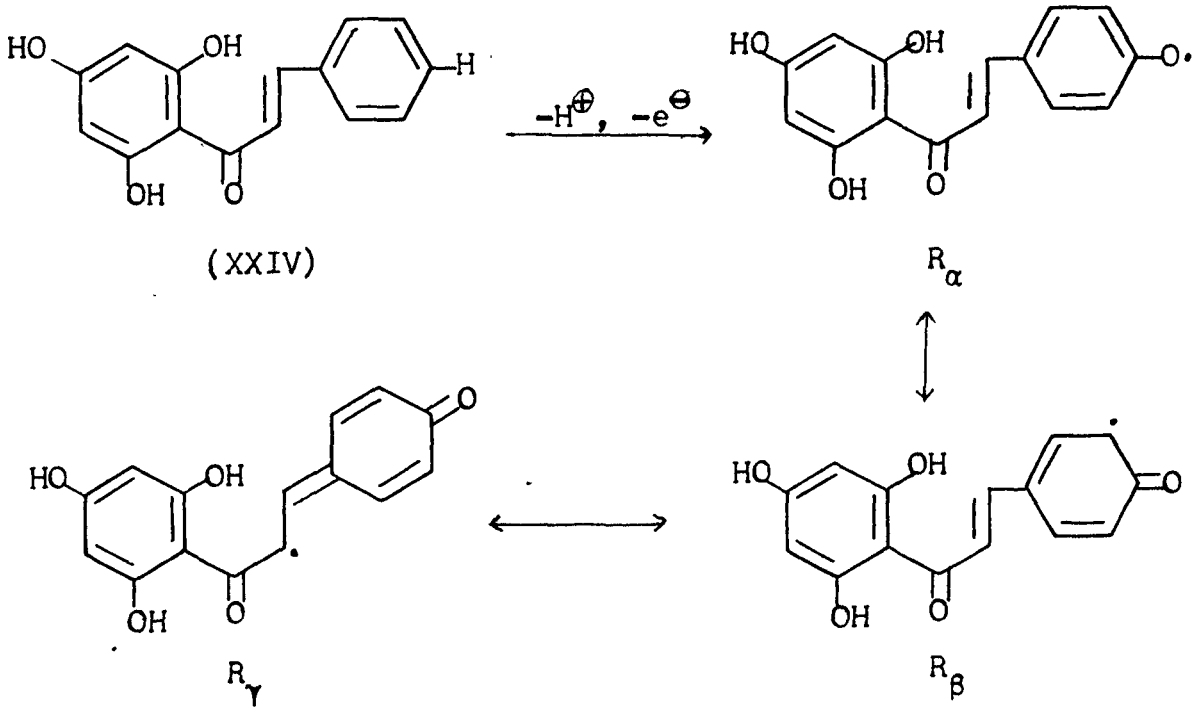


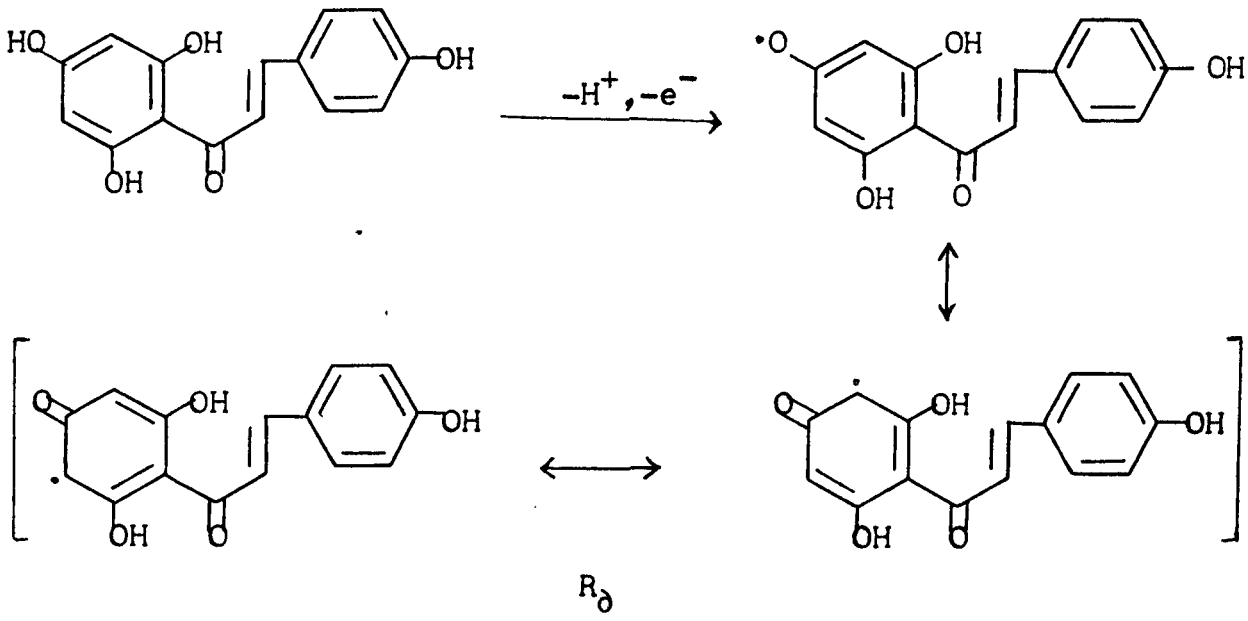
Fig. 15

The mechanism of formation of ring C in the anthocyanidins has still many obscure points. Haslam's hypothesis[59] on the anthocyanidin and catechin biosynthesis is the most widely accepted one and strictly correlates the biosynthesis of anthocyanidins with that of catechins (Fig.-15).

The formation of biflavonoids, despite the range of biflavonoids now known, may be explained in terms of oxidative coupling of two chalcone units and subsequent modification of C_3-chain[8]. Abstraction of an electron from the C-4 anion of naringeninochalcone (XXIV) affords a radical which may be represented by the canonical formulae R_α, R_β and R_γ.

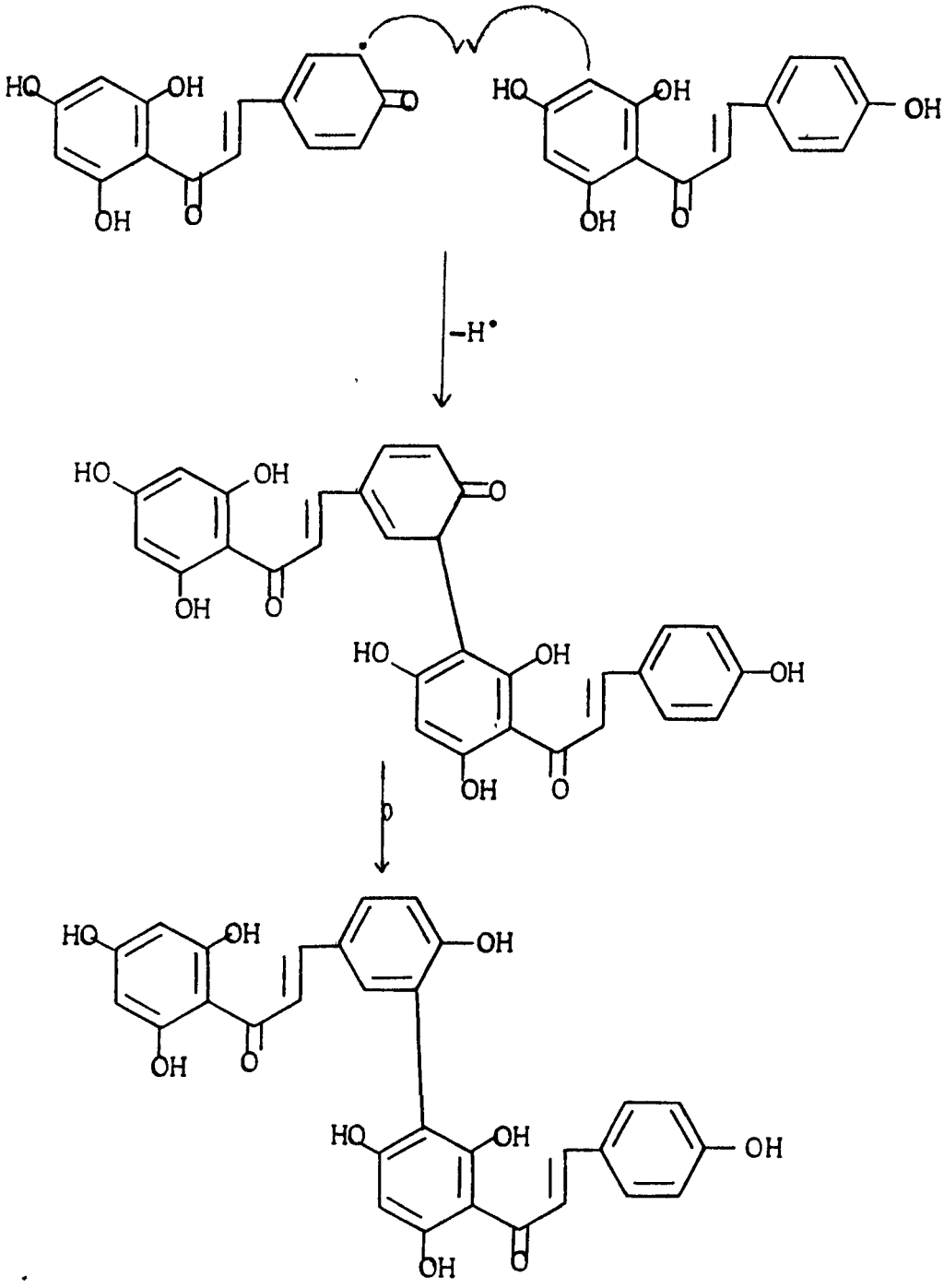


While the abstraction of an electron from the C-4' anion of XXIV will give another radical, which may be represented by several canonical formulae. However, the only canonical formula which is important in the biosynthesis of most of biflavonoids is R_∂. The formation of all the natural biflavones can be explained by appropriate pairing of these radicals.



R_∂

An alternative to the radical pairing process is the possibility of electrophilic attack of one of the above mentioned radicals upon the phloroglucinol nucleus of a chalcone or flavanone[60] which would account for the fact that in most known naturally occurring biflavonoids at least one 6- or 8-position is involved in the interflavonoidic linkage.

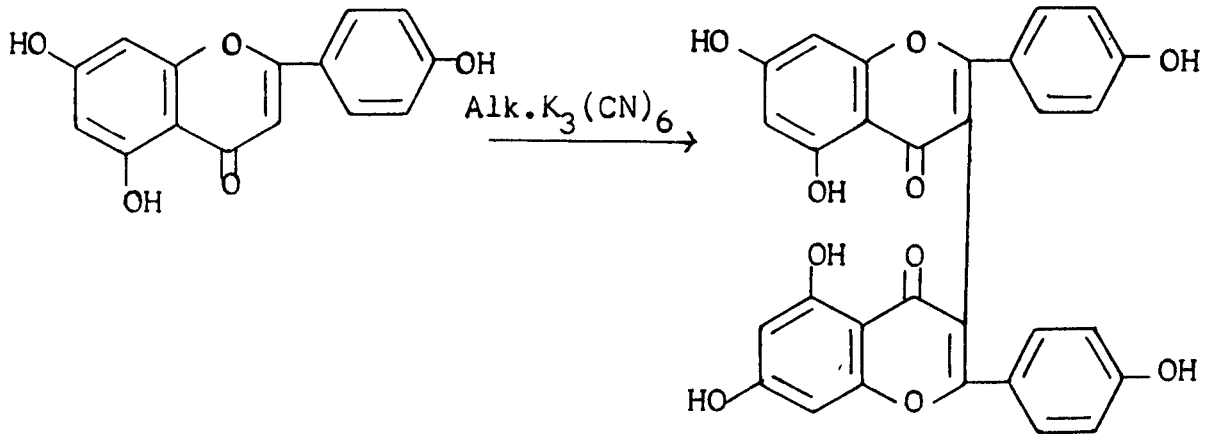

HO
OH
OH
O
HO
OH
OH
O
OH
-H•
HO
OH
OH
O
O
HO
OH
OH
O
OH
HO
OH
OH
O
OH
HO
OH
OH
O
OH

DISCUSSION

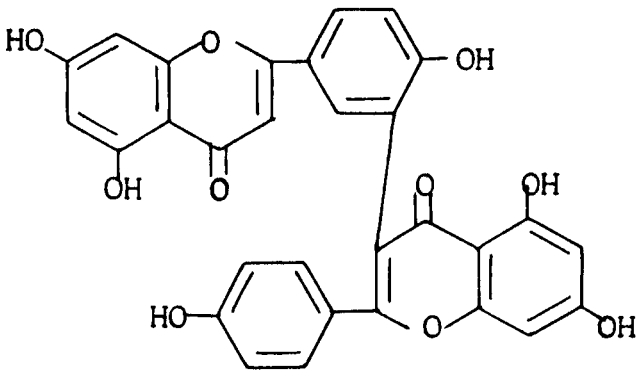
Synthetic studies carried out in the field of biflavonoids were aimed either at the synthesis of naturally occurring biflavonoids or at the preparation of biflavonoids of purely synthetic value[61-63]. The efforts, however, remained restricted to the synthesis of members of a few biflavone families where the Ullmann coupling comprises the major route[64,65]. The Ullmann coupling reaction has been employed in two ways. The one involves the coupling of the iodinated monoflavones[64] while the other involving the preparation of suitably substituted biphenyl derivatives followed by their heteroannulation[65]. The synthesis of biflavonoids with reduced heterocyclic rings poses the problems of stereochemistry and offers a greater challenge to the chemists.

The oxidative coupling of free radical species derived from phenolic substrates is now widely accepted as the pathway by which variety of natural products are biosynthesized. Such a route has also been suggested as being involved in the biogenesis of biflavonoids[60]. Synthesis of biflavonoids by oxidative coupling of hydroxy flavonoid derivatives offers the most structurally and aesthetically pleasing route, since it most closely follows the process which is believed to occur in nature. The application of the phenol oxidation in the field of biflavonoids is, however, little explored, although it has proved fruitful in other classes of natural products. There are only sporadic reports[66] on the synthesis of biflavonoids by the oxidation of hydroxy flavonoid derivatives and the results are not so encouraging as in other fields.

Molyneux and coworkers[67] first investigated the oxidative coupling of apigenin (VI) using alkaline potassium ferricyanide to determine whether the resulting product or products exhibit the same mode of coupling as those occurring in natural biflavonoids. Thus, oxidation of apigenin with alk. $K_3Fe(CN)_6$ afforded two biflavones with C-3'/C-3 (XXV) and C-3/C-3 (XXVI) interflavone linkages which arise presumably by appropriate spin pairing of the mesomeric radicals, XXVIII and XXIX (Fig.16). The biflavone with C-3'/C-3 linkage is now known to occur in nature[68].



+ (XXVI)



(XXV)

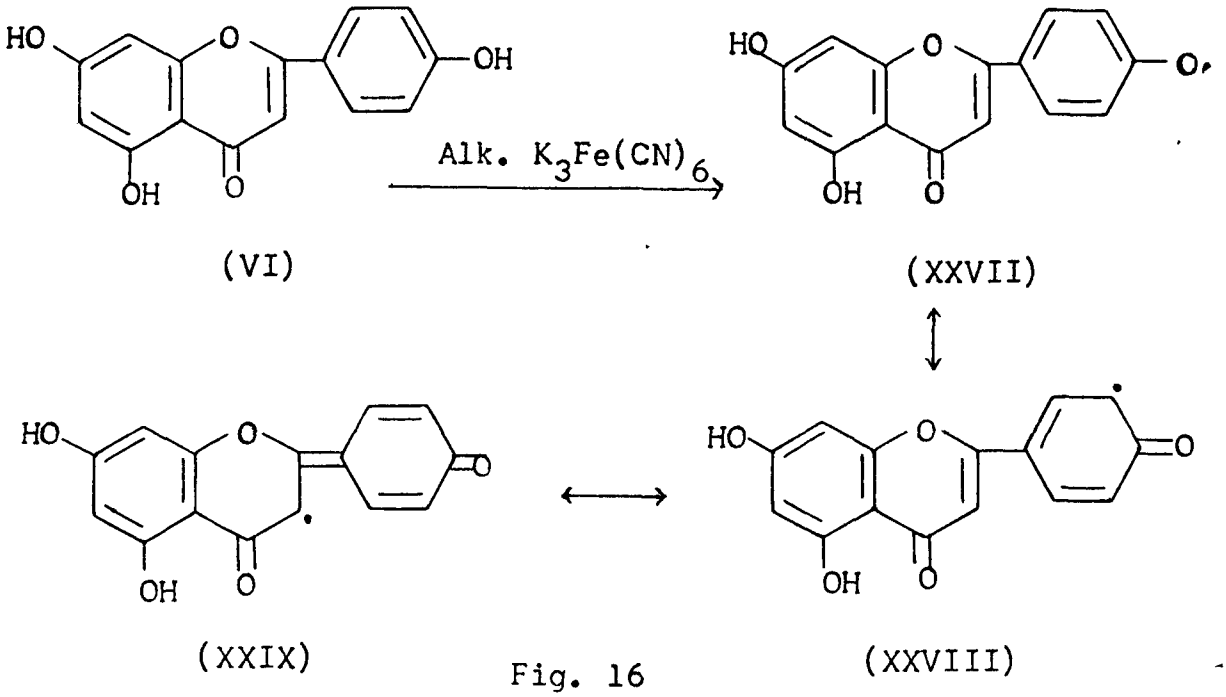


Fig. 16

Electron spin resonance (ESR) studies have shown that delocalization of an unpaired electron initially generated at the C-4' hydroxy group in apigenin occurs only in rings B and C[69] (Fig.16). The coupling of the mesomeric radicals, XXVII-XXIX, thus, can not explain the formation of natural biflavones involving ring A in the linkage such as, cupressuflavone, agathisflavone and succedaneaflavone (Fig.4). However, if a free radical were to be generated at either of the hydroxy groups on the ring A of apigenin and delocalized (Fig.17), appropriate radical pairing would explain the formation of natural biflavones involving ring A in the linkage.

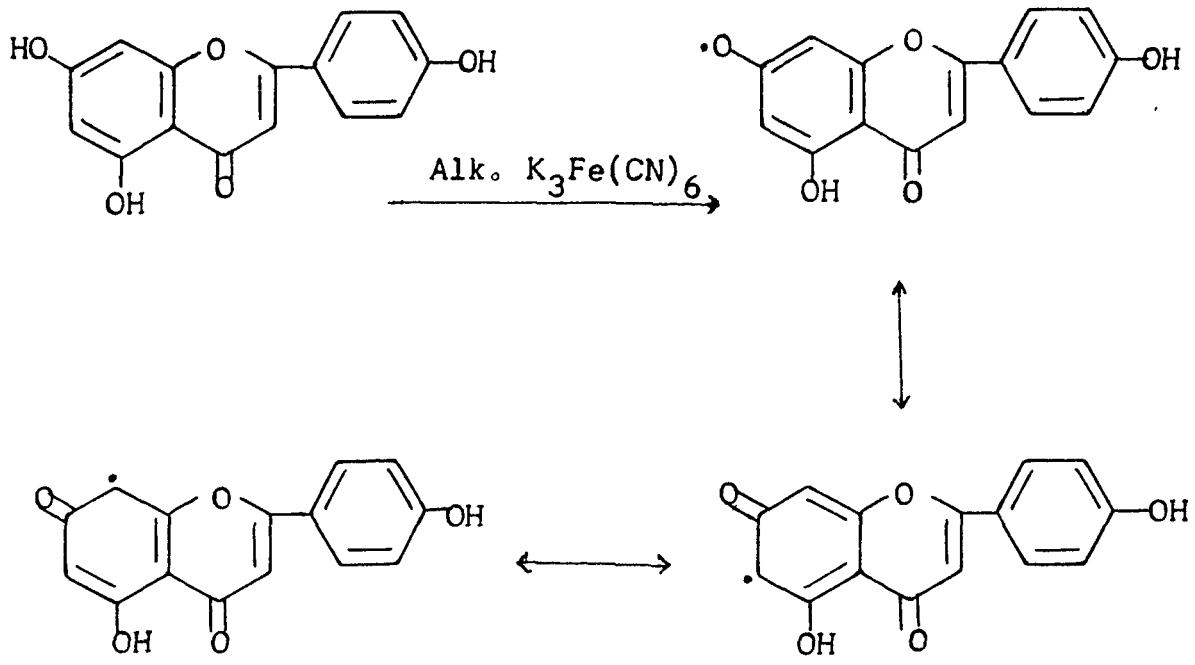
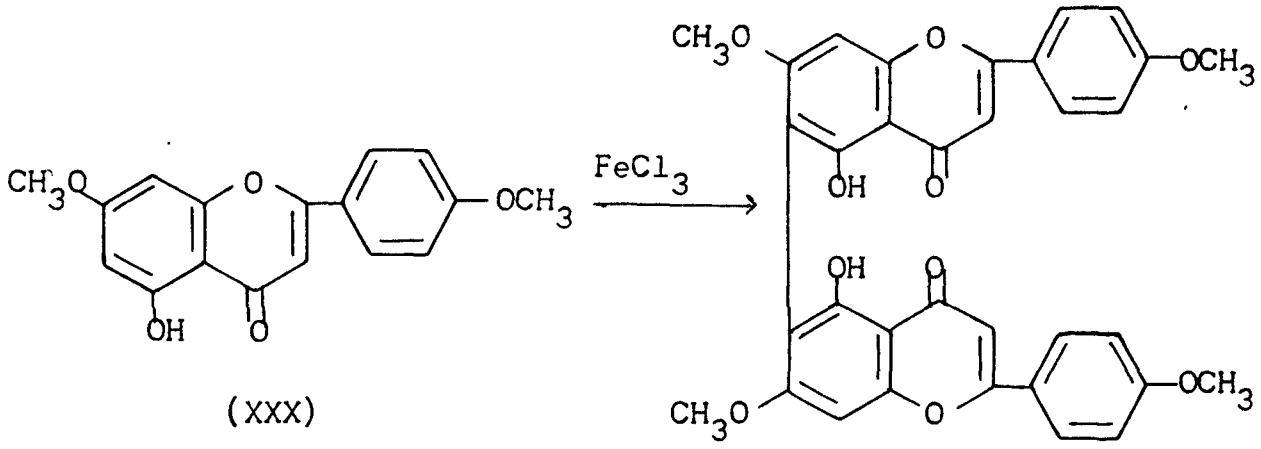


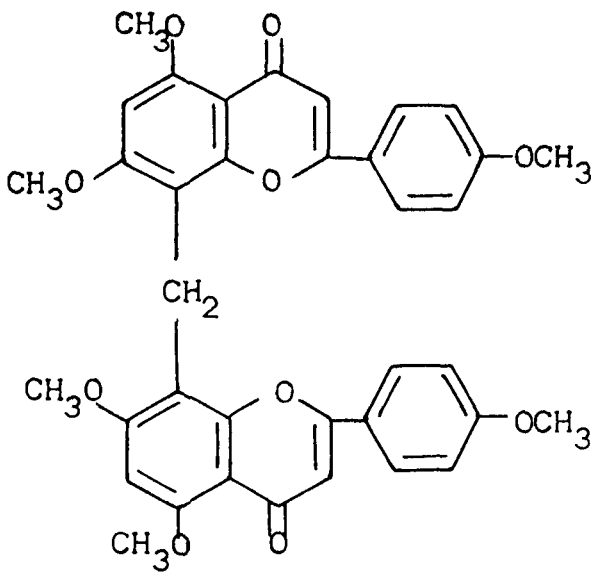
Fig. 17

There is, however, no experimental evidence for the fact that a radical can be generated at ring A of apigenin. Natarajan et al.[70] carried out oxidation experiment which suggested that radical can be generated at ring A of an apigenin derivative provided that the C-4' and C-7 hydroxy groups are methylated. Thus, oxidative dimerization of apigenin 4',7-dimethyl ether (XXX) with ferric chloride in boiling dioxane has been reported to give a product in 6% yield whose properties suggested that to be a C-6/C-6 coupled biflavone (XXXI).

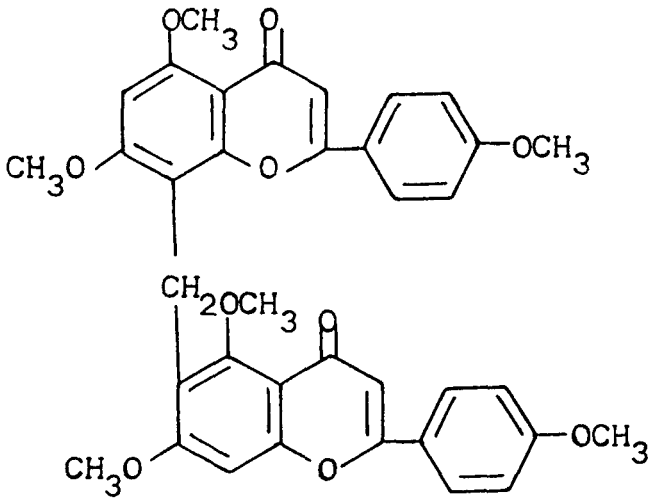


(XXX) (XXXI)

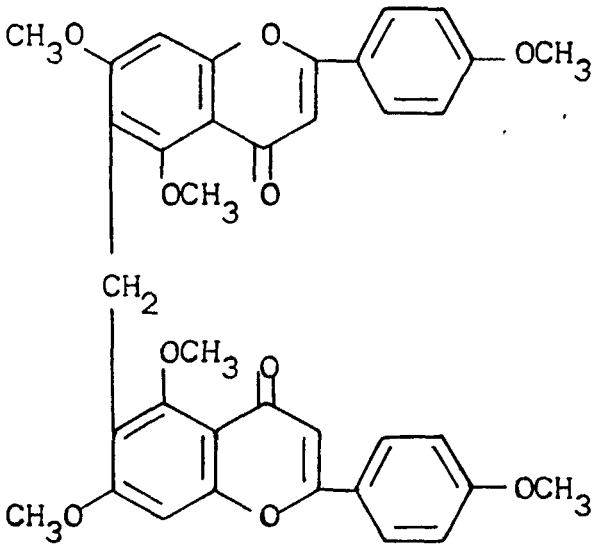
However, Murti et al.[71] reinvestigated the reaction of apigenin-4',7-dimethyl ether (XXX) with ferric chloride in dioxane and isolated unexpectedly three products, characterized as their permethyl ethers, as hexamethyl ethers of homocupressuflavone (XXXII), homoagathisflavone (XXXIII) and homosuccedaneaflavone (XXXIV).



(XXXII)



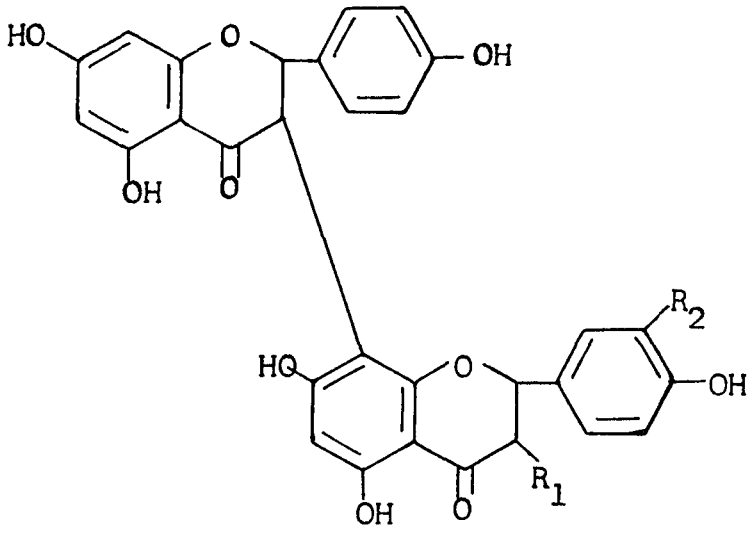
(XXXIII)



(XXXIV)

Literature does not record, to the best of our knowledge, any report on the oxidative dimerization of either a hydroxyflavanone or a hydroxychalcone[66], though the oxidation of chalcones and flavanones has been studied extensively[72,73]. The products of oxidation of chalcones and flavanones are either flavones, aurones or isoflavones.

Proposal for the biogenesis of biflavonoids from chalcones was put forward by Jackson and coworkers[74]. They isolated biflavanones (XXXVa-d) with C-3/C-8(C-6) linkage from natural source.



(XXXV)

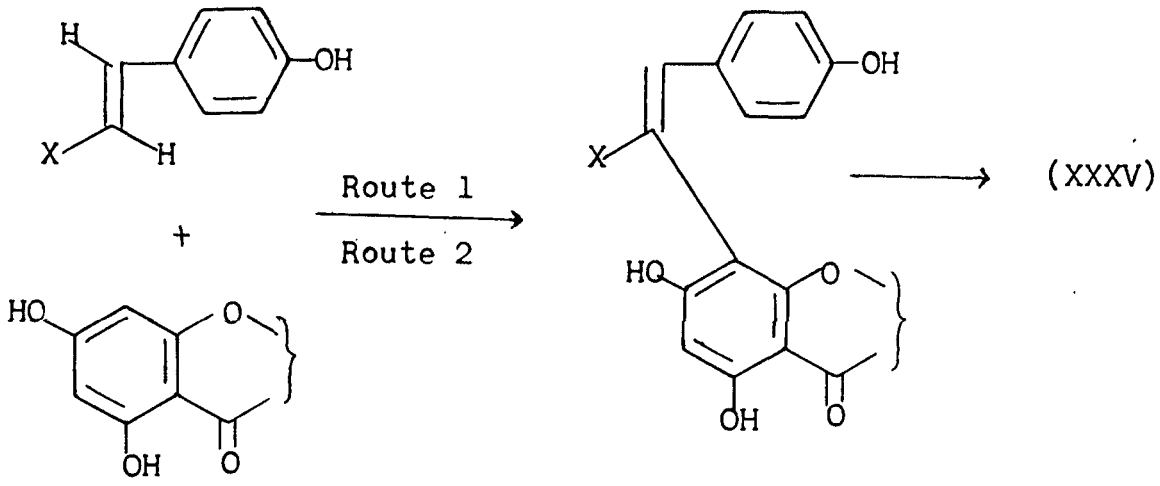
(a) GB-1 ; R_1= OH, R_2= H

(b) GB-1a; R_1= R_2= H

(c) GB-2 ; R_1= R_2= OH

(d) GB-2a; R_1= H, R_2= OH

The biogenesis of these biflavanones has been envisaged by either radical pairing or radical substitution of two complete or embryonic flavanone units in which a quinone methide radical combines with an aryl system.



X= -COOH, 2,4,6-trihydroxybenzoyl etc.

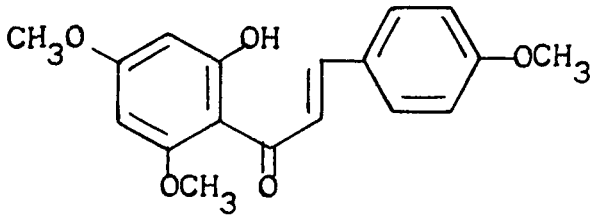
Route 1. (i) hydrogen abstraction (ii) radical pairing (iii) enolization (iv) further extension of flavanone synthesis if possible.

Route 2. (v) hydrogen abstraction from chalcone precursor (vi) radical substitution (vii) loss of H atom (viii) enolization.

The possible role of the chalcones in the biogenesis of biflavonoids and the lack of evidence in favour of existence of radical on ring A prompted us to study the reaction of some 2'-hydroxychalcones with metal-ion oxidants. The chalcones selected for the study are those having oxygenation pattern most abundant in nature. The results of the reactions of 2'-hydroxychalcones with silica bound ferric chloride, copper(II) acetate-perchloric acid-acetic acid reagent system and $[Fe(DMF)_3Cl_2][FeCl_4]$ are described in this part.

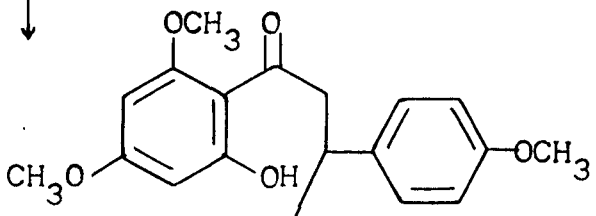
Reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI) with silica bound ferric chloride

The reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone with silica bound ferric chloride was performed in the following manner. 2'-Hydroxy-4,4',6'-trimethoxychalcone (XXXVI) was dissolved in dichloromethane and added to ferric chloride adsorbed on silica gel. The solvent was removed under reduced pressure and the reaction mixture was stirred for six hours. The reaction was worked up to afford a gummy mass which was subjected to column chromatography. Unreacted 2'-hydroxy-4,4',6'-trimethoxychalcone was recovered when the column was run with petrol:benzene (1:1). Elution of the column with different solvent systems afforded four products. The major product was characterized as I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4',I-6',II-6'-hexamethoxy-[I-β, II-3']-dihydrobichalcone (XXXVII). Of the three minor products, one compound was partially identified as I-2',II-2'-dihydroxy-I-4, II-4,I-4',II-4',I-6',II-6'-hexamethoxy-[I-3', II-3']-bichalcone (XXXVIII). Two other products, XXXIX and XL, could not be fully characterized. Large amount of polymeric products was obtained when the column was eluted with ethyl acetate and methanol.

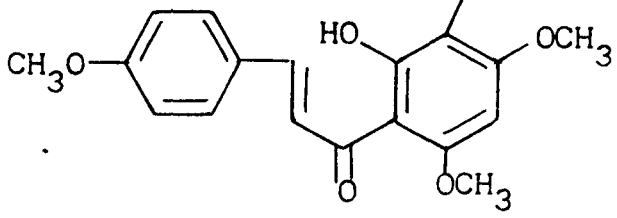


(XXXVI)

$FeCl_3/SiO_2$

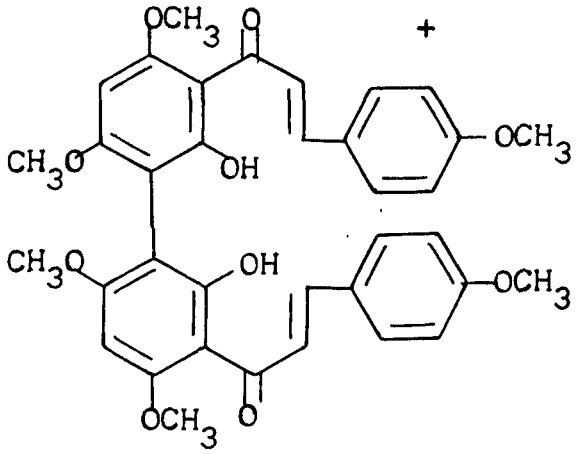


(XXXIX) + (XL) +



+

Polymeric mixture (XXXVII)



(XXXVIII)

Characterization of I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4', I-6',II-6'-hexamethoxy-[I-β, II-3']-dihydrobichalcone (XXXVII)

The compound melting at 222-4°C exhibited, in its mass spectrum, the molecular ion, $M^{+\cdot}$, peak at m/z 628 (18.44%) which was indicative of it being a derivative of the dimer of 2'-hydroxy-4,4',6'-trimethoxychalcone. The compound gave brown colour with alcoholic ferric chloride and dark red colour with conc. H_2SO_4[3c] suggesting the presence of phenolic group and chalcone moiety in the compound. The band at 3450 cm^{-1} in the i.r. spectrum confirmed the presence of phenolic group. The carbonyl stretching band was observed at 1620 cm^{-1}. The lowering of carbonyl frequency was due to the hydrogen bonding with the neighbouring phenolic group. U.v. spectrum of this compound showed two maxima at 290 and 365 nm. The band II at 365 nm is the characteristic band of the chalcone[8c] and provided further evidence in favour of chalcone moiety in the compound. The band at 290 nm was due to the benzoyl moiety. It can be concluded on the basis of its i.r., u.v. spectra in conjunction with the molecular ion peak that the compound may be a dihydrobichalcone. The structure was further elucidated with the help of n.m.r. and mass spectra.

The n.m.r. spectrum (Fig.18) exhibited two singlets in the lowest field at δ 14.25 and 13.86 each for one proton which were ascribable to the phenolic protons. Signals for the six

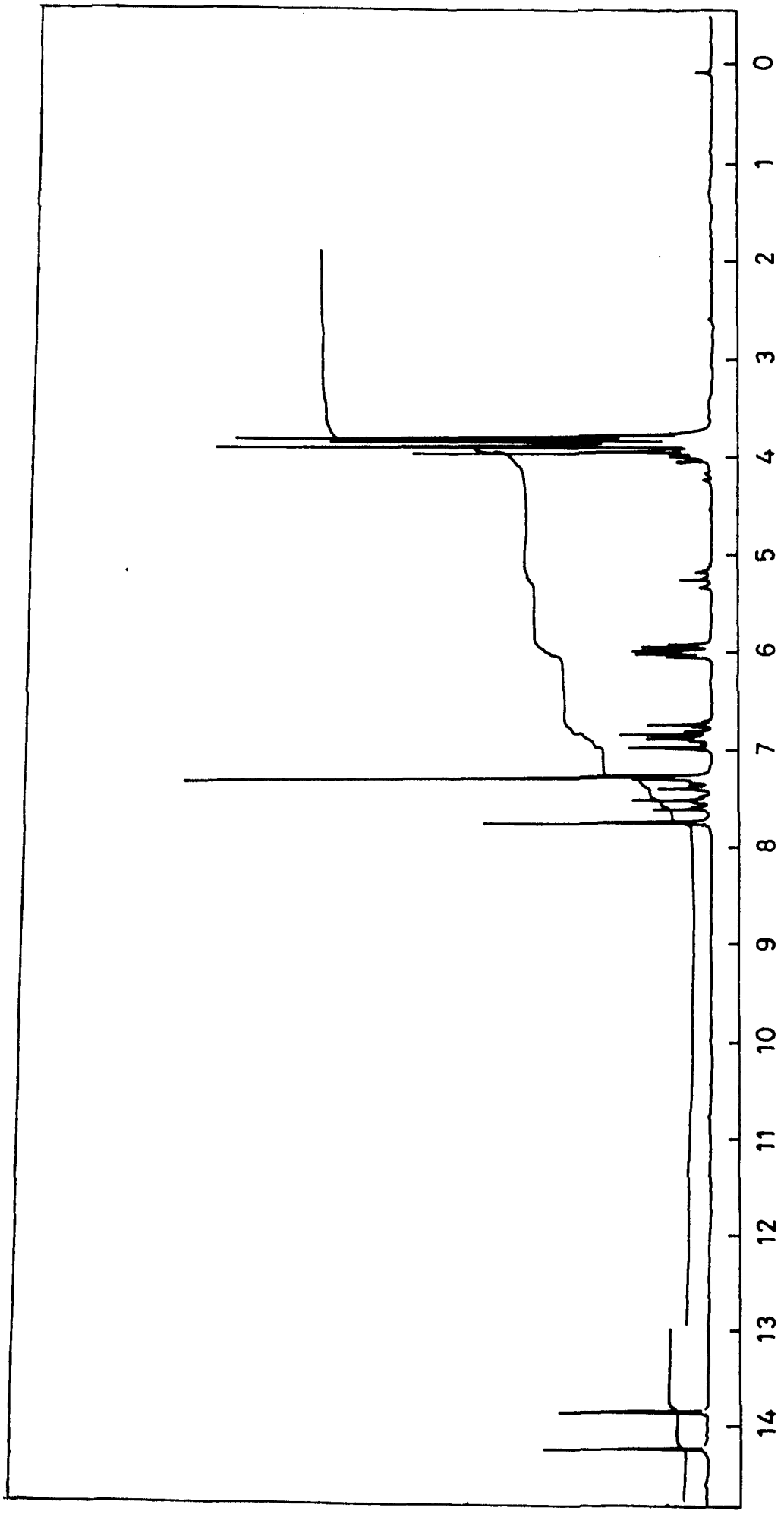
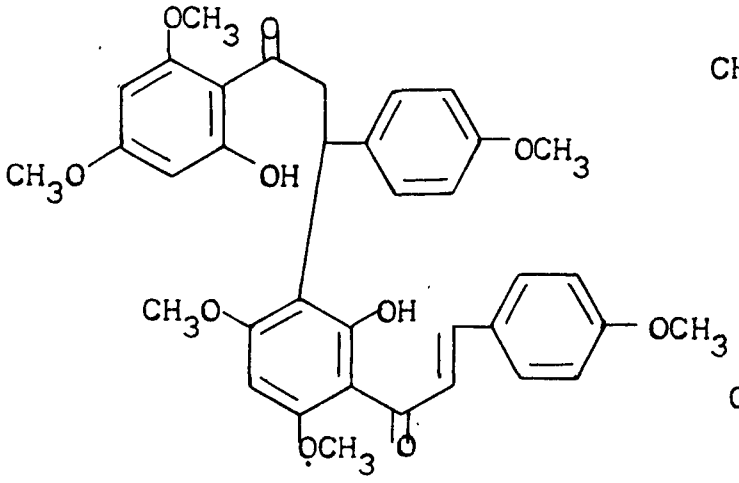


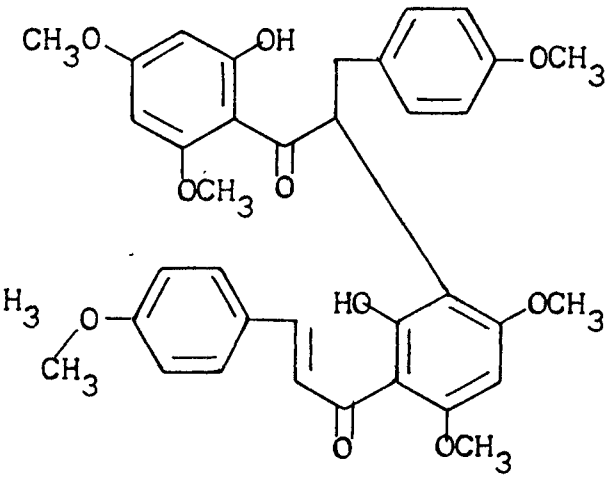
FIG. 18

methoxy groups were seen as a compact group within the range ∂ 3.68-3.92. Aromatic region of the spectrum displayed a singlet at ∂ 7.76 for two olefinic protons of the chalcone unit as seen in the model compound, 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI)[10]. A pair of A_2B_2 or more accurately AA'BB'[75] showed the presence of two 1,4-substituted benzene rings. The doublets of two protons each at ∂ 6.79 and 7.35 (J=9 Hz) were assigned to I-3,5-H and I-2,6-H, respectively, while another set of doublets at ∂ 6.92 and 7.55 (J=9 Hz) was assigned to II-3,5-H and II-2,6-H, respectively. The possibility of involvement of any of the rings B in the linkage was, therefore, ruled out. At slightly higher field, there was a group of three signals which, as indicated by chemical shift and proton count, belonged to three protons located on the two electron rich phloroglucinol derived rings. The fact that there were three and not four such protons was decisive, for it indicated that only one ring A was involved in the linkage. Of the three shielded signals, two meta coupled doublet at ∂ 5.90 and 6.02 (J=3 Hz) were assigned to I-3' and I-5' protons of dihydrochalcone unit. A one proton singlet at ∂ 5.99 can be attributed to either C-3' or C-5' proton of chalcone unit. This signal was, however, assigned to the C-5' proton as it was more close the chemical shift of the C-5' proton in 2'-hydroxy-4,4',6'-trimethoxychalcone. The signals for the three aliphatic protons of the dihydrochalcone unit were observed as a doublet at ∂ 4.00 (J=8 Hz) for methylene protons and a triplet at ∂ 5.28 (J=8 Hz) for one methine proton. The

chemical shifts of protons of compound, XXXVII are shown in table I. It can be inferred, on the basis of n.m.r. spectroscopy, that linkage is either [I-β, II-3'] (XXXVII) or [I-α, II-3'] (XLI).



(XXXVII)



(XLI)

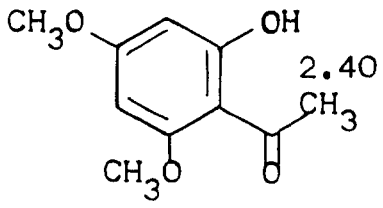
Of the two possible linkages, the compound was assigned the linkage as [I-α, II-3'] on the basis of n.m.r. data comparison. The signal for the acetyl protons in phloroacetophenone-4,6-dimethyl ether (XLII)[76] appears at δ 2.40, while the signal for the methylene protons in the n.m.r. spectrum of chalcone (XLIII)[74] resonates at δ 4.38. It can be said that 2'-hydroxy-4,4',6'-trimethoxychalcone when bonded to acetyl carbon of (XLII) through C-3', has a down-field effect of about 2.0 ppm on the chemical shift of methylene protons. Also, the α-methylene protons in the n.m.r. spectrum of 2'-hydroxy-4,4',6'-trimethoxydihydrochalcone (XLIV)[76] appear as a

Table-I: Chemical shifts of protons of I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4',I-6',II-6'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XXXVII).

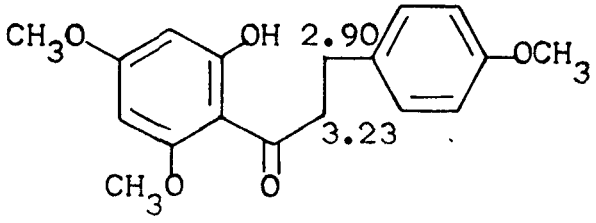
Proton assignment	Chemical shifts (δ ppm)
MeO-I-4	3.68 (s, 3H)
MeO-II-4	3.80 (s, 3H)
MeO-I-6'	3.81 (s, 3H)
MeO-I-4',II-6'	3.85 (s, 6H)
MeO-II-4'	3.92 (s, 3H)
H-I-α	4.00 (d, J=8 Hz, 2H)
H-I-β	5.28 (t, J=8 Hz, 1H)
H-I-3'	5.90 (d, J=3 Hz, 1H)
H-II-5'	5.99 (s, 1H)
H-I-5'	6.02 (d, J=3 Hz, 1H)
H-I-3,5	6.79 (d, J=9 Hz, 2H)
H-II-3,5	6.92 (d, J=9 Hz, 2H)
H-I-2,6	7.35 (d, J=9 Hz, 2H)
H-II-2,6	7.55 (d, J=9 Hz, 2H)
H-II-α,β	7.76 (s, 2H)
HO-I-2'	13.86 (s, 1H)
HO-II-2'	14.25 (s, 1H)

s= singlet, d= doublet, t= triplet; Spectrum run in $CDCl_3$ at 100 MHz and TMS as internal standard δ= 0.00.

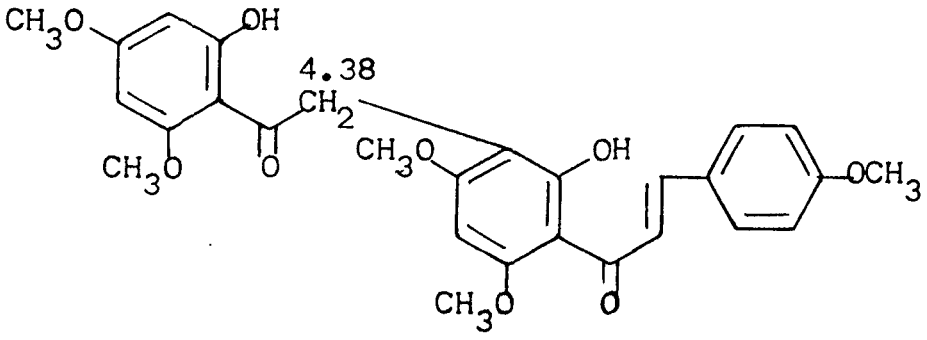
triplet at δ 3.23, while the signal for β-methylene protons appears at δ 2.90.



(XLII)



(XLIV)

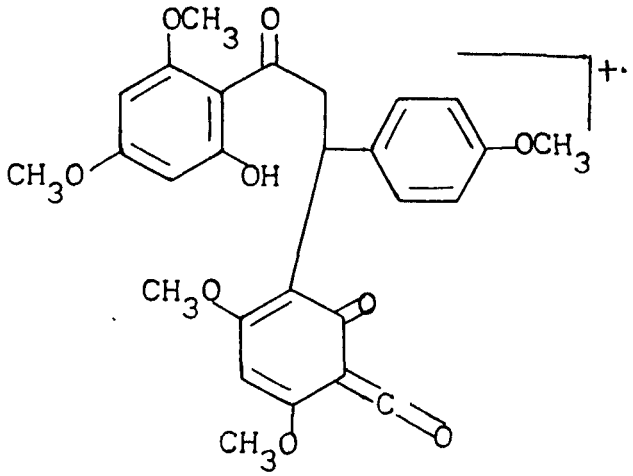


(XLIII)

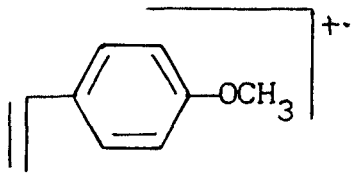
In the light of these observations, the expected values for the chemical shifts of the protons on the C_α in [I-α, II-3']-dihydrobichalcone (XLI) and on the C_β in [I-β, II-3']-dihydrobichalcone (XXXVII) should have been around δ 5.23 and 4.90, respectively. The signal for the methine proton on the C_3-unit was seen as a triplet centred at δ 5.28. The compound was, therefore, characterized as I-2',II-2'-dihydroxy-I-4,II-4,I-4', II-4',I-6',II-6'-hexamethoxy-[I-α, II-3']-dihydrobichalcone (XLI).

The structure of this compound was later revised to I-2', II-2'-dihydroxy-I-4,II-4,I-4',II-4',I-6',II-6'-hexamethoxy-[I-β, II-3']-dihydrobichalcone (XXXVII) in the light of plausible mechanism of this reaction. The mechanism will follow at the end of the discussion.

The mass spectrum of the compound (Fig.19) also proved helpful in the structural assignment. The fragmentation pattern (Chart-I) is typical as that for chalcones and dihydrochalcones. The molecular ion peak appeared at m/z 628. Retro-Diels-Alder fragmentation of chalcone unit afforded two fragments at m/z 494 and 134. These fragments suggested the linkage of chalcone unit through ring A.



m/z 494



m/z 134

The linkage of the chalcone unit through ring A was further supported by an ion at m/z 161. Another characteristic ion in the spectrum was seen at m/z 121. The linkage of the

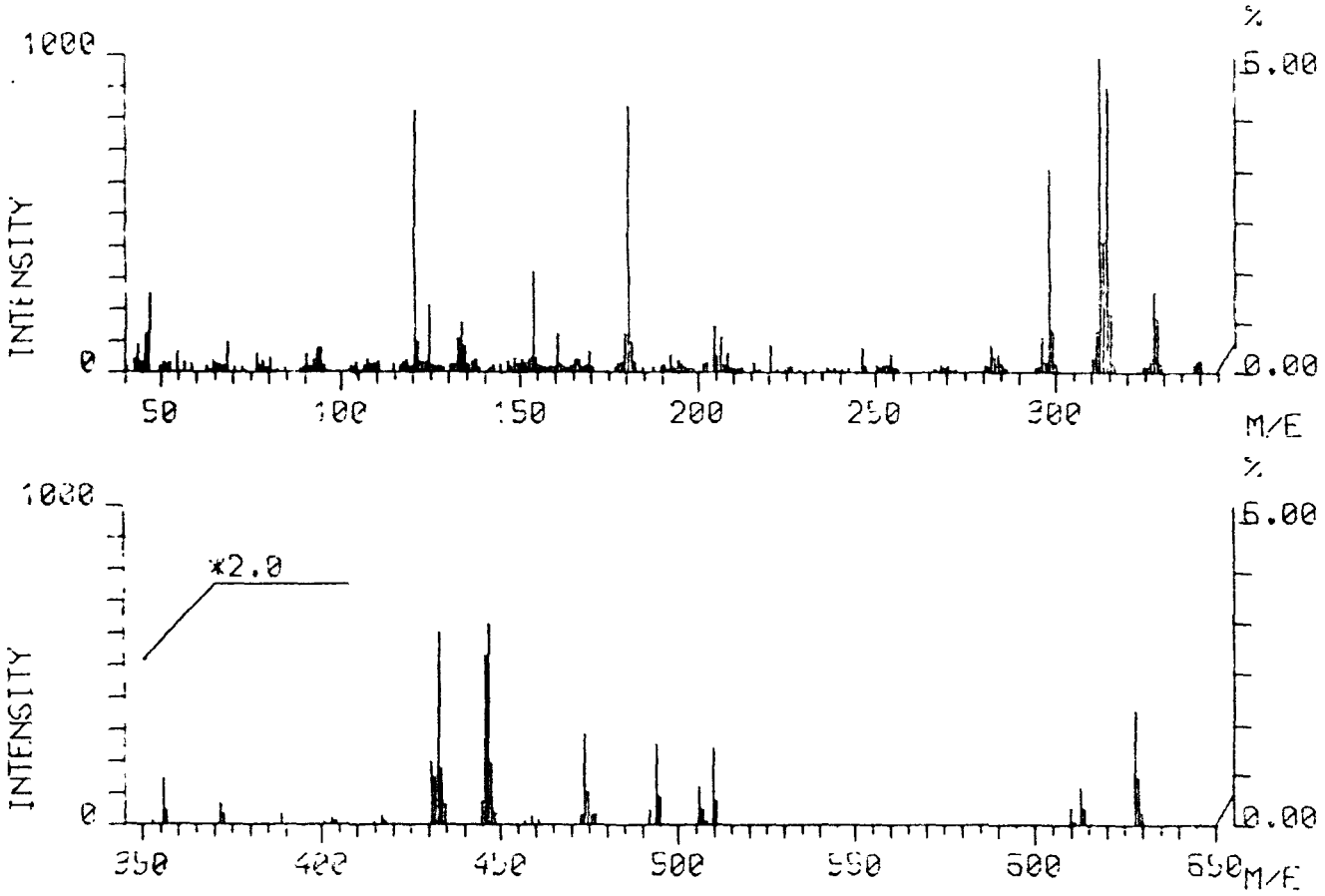
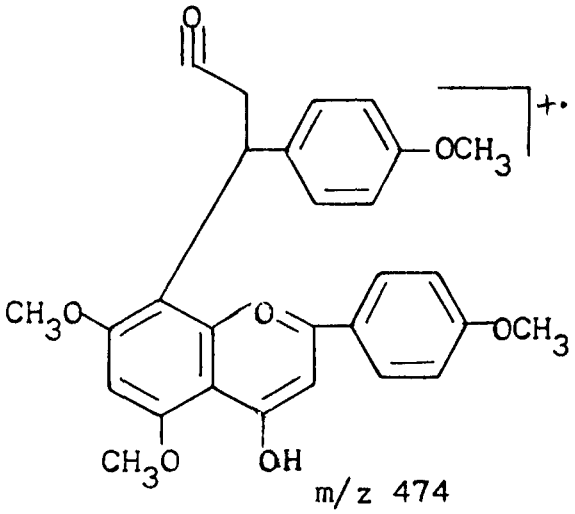
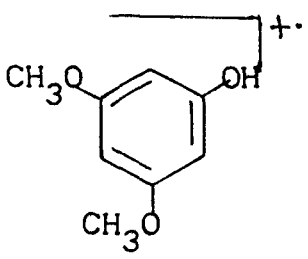

1000
INTENSITY
0
%
5.00
0.00
50
100
150
200
250
300
M/E
1000
INTENSITY
0
*2.0
%
5.00
0.00
350
400
450
500
550
600
650
M/E

Fig. 19

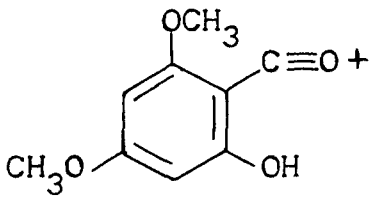
dihydrochalcone unit through C_3-unit was supported by the ions at m/z 474 and 447. The loss of ring A from the dihydrochalcone unit afforded fragments at m/z 474 and 154. While the loss of benzoyl group from the molecular ion gave fragment at m/z 447 alongwith the benzoyl cation at m/z 181. These fragments provided evidence in favour of non-involvement of ring A of dihydrochalcone unit in the linkage.



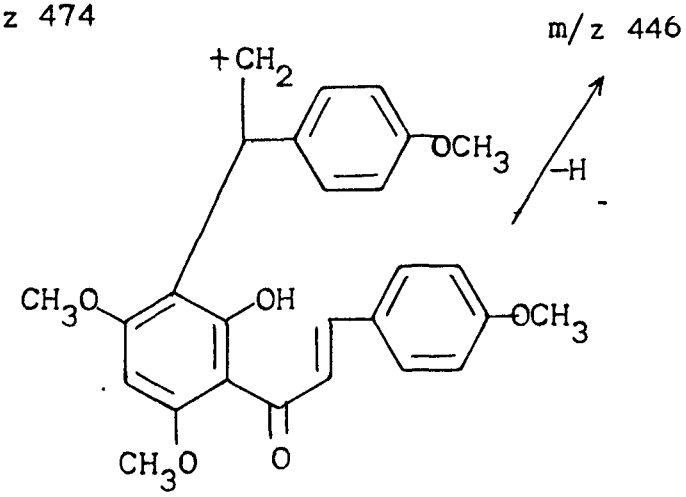
m/z 474



m/z 154



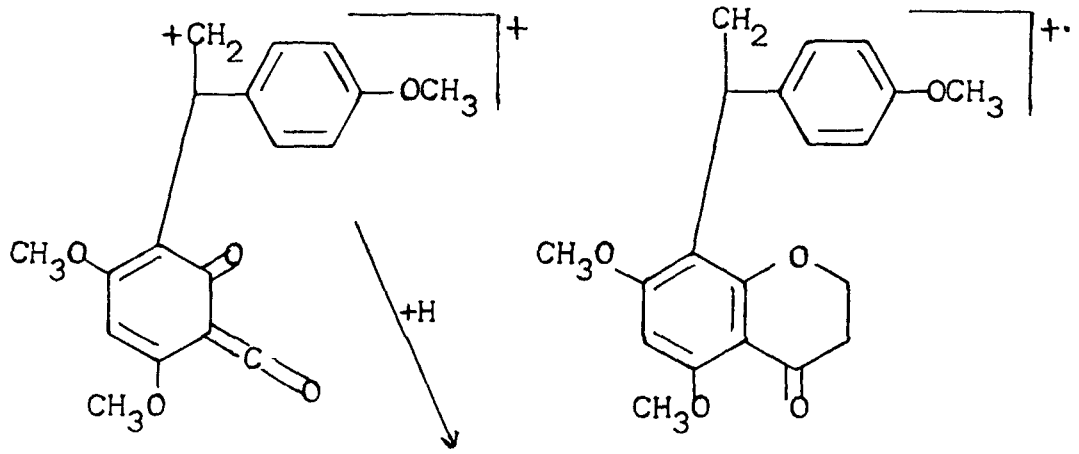
m/z 181



m/z 446

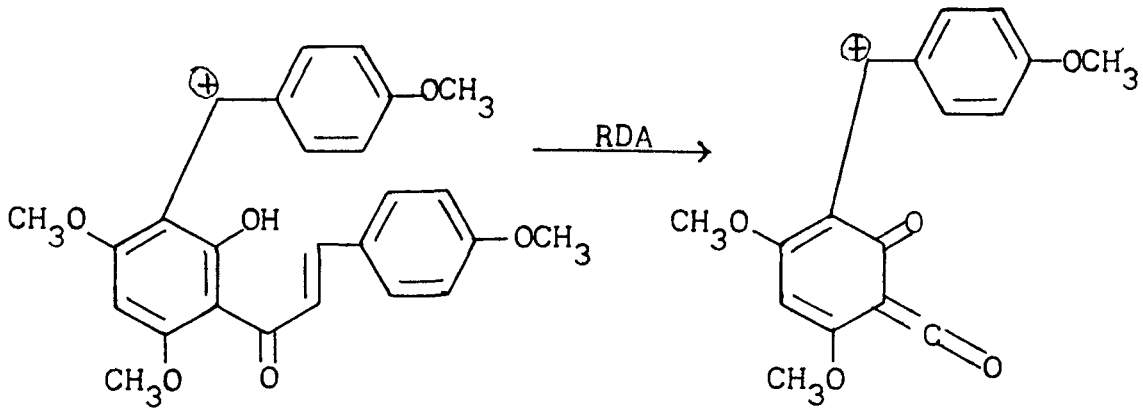
m/z 447

The RDA fragmentation of the intact chalcone unit of the ion at m/z 447 and the loss of ring B from this ion may have afforded two structurally diagnostic peaks at m/z 313 and 340. However, the peak at m/z 313 appeared as base peak and doubly charged $(M-2H)^{++}$ ion might also be contributing to this peak.



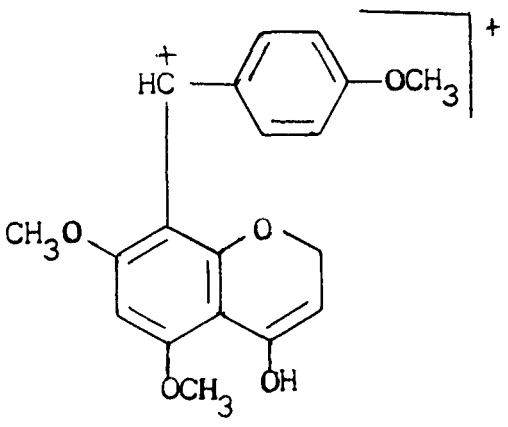
m/z 313 m/z 314 m/z 340

The most structurally characteristic peaks in the spectrum were at m/z 433 and 299. These fragments supported the linkage of the dihydrochalcone unit through β carbon. The RDA fragmentation of the ion at m/z 433 afforded fragment at m/z 299.



m/z 433 m/z 299

The formation of an ion at m/z 327 may be explained in terms of loss of ring B from the ion at m/z 433. The fragments at m/z 433, 299 and 327 can best be explained if the linkage of the dihydrochalcone unit is through β carbon. Other prominent peaks in the spectrum were at m/z 328, 314, 298 and 180.



m/z 327

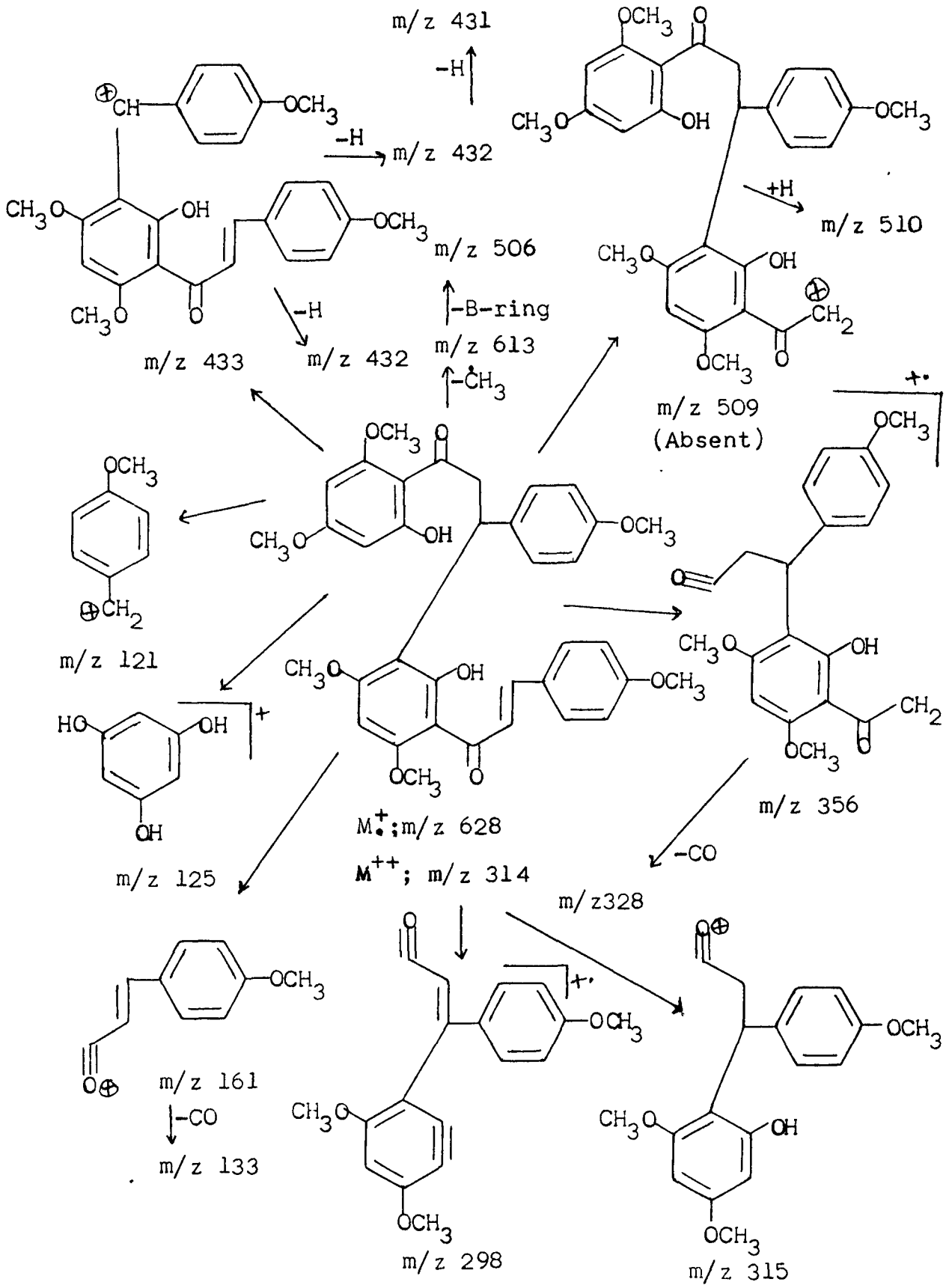

m/z 431
-H
-H
m/z 432
m/z 506
m/z 433
-H
m/z 432
-B-ring
m/z 613
-CH3
+H
m/z 510
m/z 509
(Absent)
m/z 121
m/z 125
M+•;m/z 628
M++; m/z 314
m/z 356
-CO
m/z328
m/z 161
-CO
m/z 133
m/z 298
m/z 315

Chart I

Partial characterization of I-2',II-2'-dihydroxy-I-4,II-4, I-4',II-4',I-6',II-6'-hexamethoxy-[I-3',II-3']-bichalcone (XXXVIII)

The compound, m.p.288-90°C, showed in the mass spectrum, the molecular ion peak at m/z 626 suggesting it to be a dehydro-dimer of 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI). The compound gave positive ferric chloride test and dark red colouration with conc. H_2SO_4. The presence of phenolic group was confirmed by the band at 3450 cm^{-1} in the i.r. spectrum. The absence of flavanone moiety in the compound was indicated by the carbonyl stretching band at 1620 cm^{-1}. Ultra-violet spectrum exhibited bands at 228 and 350 nm confirming the presence of chalcone moiety. I.r. and u.v. spectroscopy in conjunction with the molecular ion peak led us to conclude that the compound is a bichalcone. The exact points of linkage of the two units could not be established since the n.m.r. spectrum was not obtained. However, a probable structure was elucidated with the help of its mass spectrum.

The mass spectrum (Fig.20) displayed the ring B fragments at m/z 121, 133, 134 and 161 which indicated the non-involvement of atleast one ring B in the linkage. The spectrum did not show any of the ring A fragments at m/z 180 and 181 suggesting the linkage of the two chalcone units through rings A. The linkage of the two units through A rings was further suggested by doubly charged ion

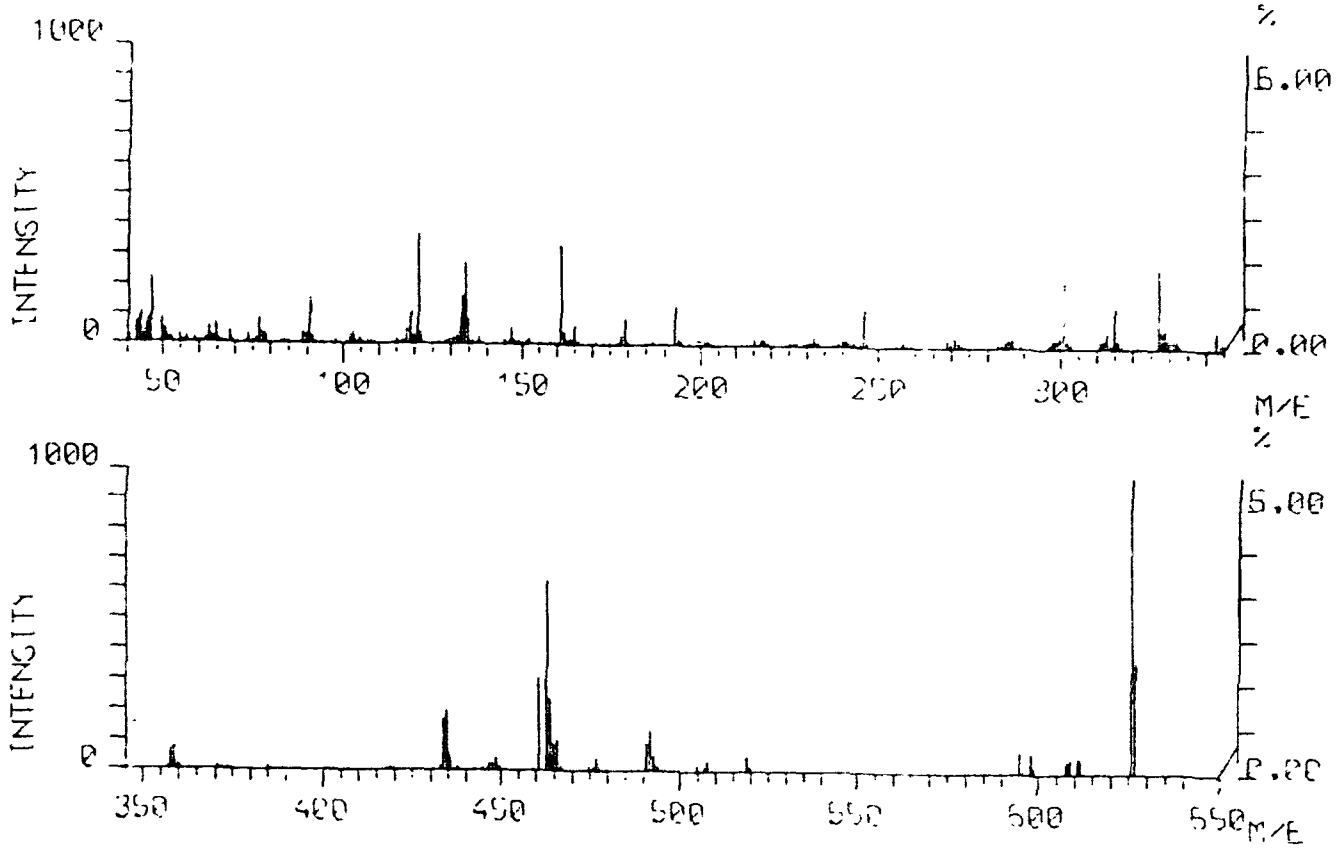

1000
INTENSITY
0
50
100
150
200
250
300
%
5.00
0.00
M/E
1000
INTENSITY
0
350
400
450
500
550
600
M/E
%
5.00
0.00

Fig. 20

at m/z 179. It is not possible to assign the linkage only on the basis of mass spectrum. There are three possible linkages, [I-3', II-3'], [I-3',II-5'] and[I-5',II-5'], which could be assigned to the compound. The bichalcones with [I-3',II-3'] and [I-5',II-5'] linkage are known. The possibility of [I-5',II-5']-bichalcone was eliminated as the melting point of our product was very high compared to that of [I-5',II-5']-bichalcone[63]. It is not possible to differentiate between the two other possible linkages on the basis of available data, however, the compound was characterized as I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4',I-6',II-6'-hexamethoxy-[I-3',II-3']-bichalcone (XXXVIII) as the melting point of our compound was same as the reported melting point of compound (XXXVIII)[65]. The fragmentation pattern of the compound (XXXVIII) is shown in chart II.

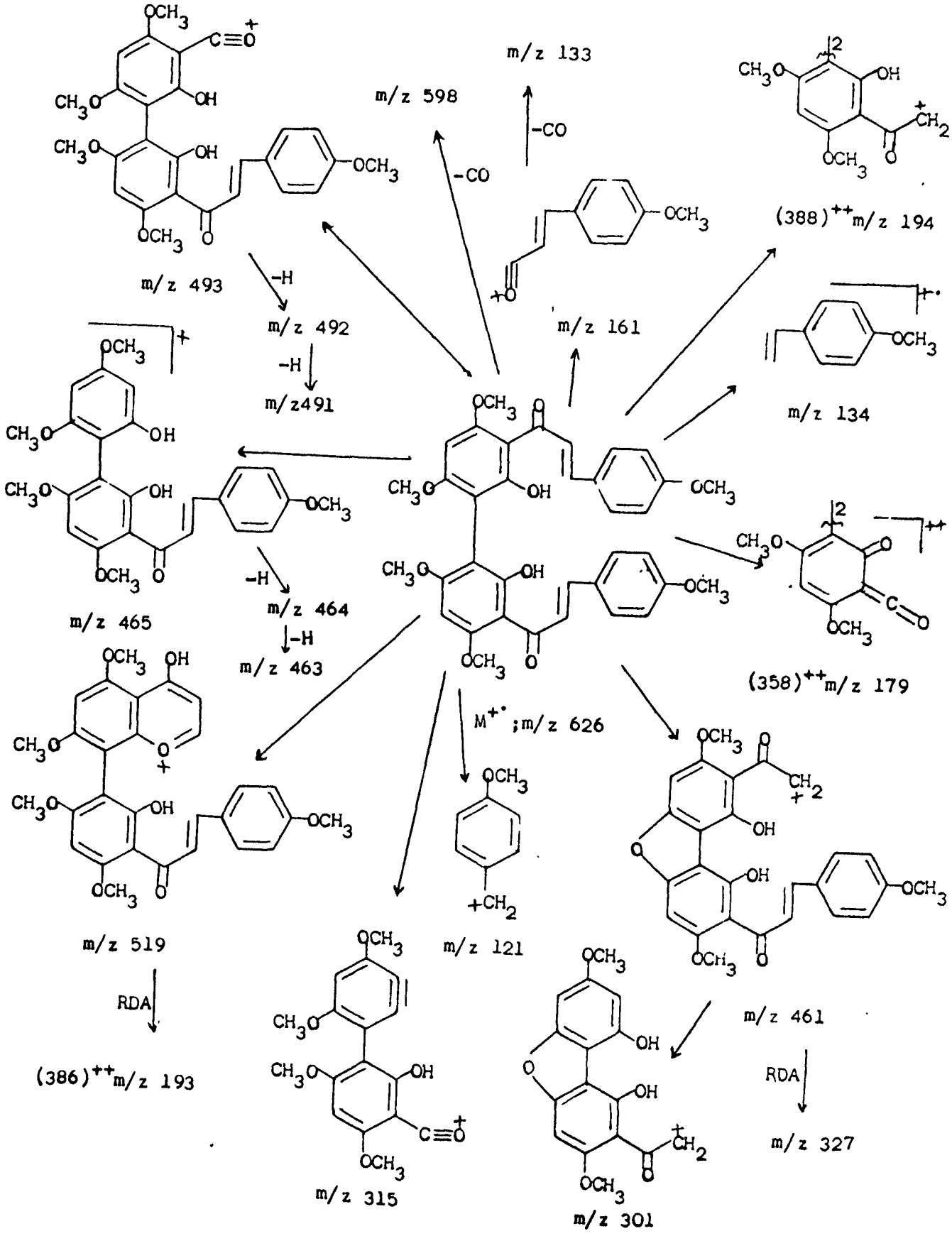

m/z 493
-H
m/z 492
-H
m/z491
m/z 598
-CO
m/z 133
-CO
m/z 161
(388)++m/z 194
m/z 134
m/z 465
-H
m/z 464
-H
m/z 463
(358)++m/z 179
M+• ;m/z 626
m/z 519
RDA
(386)++m/z 193
m/z 121
m/z 315
m/z 461
RDA
m/z 327
m/z 301

Chart II

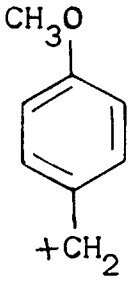
Partial characterization of compound (XXXIX)

The compound melting at 158-60°C exhibited in the infra-red spectrum, the hydroxyl stretching band at 3440 cm^{-1}, and carbonyl band at 1620 cm^{-1}, indicating the hydrogen bonding between the hydroxyl and carbonyl functionalities. The u.v. spectrum was almost identical to that of [I-β,II-3']-dihydrobichalcone (XXXVII) and showed maxima at 275 and 350 nm. Due to the insufficient amount, the n.m.r. spectrum of the compound could not be obtained. The probable structure of the compound was elucidated with the help of i.r., u.v. and mass spectra. The peak with the highest mass to charge ratio, in the mass spectrum was seen at m/z 405. The base peak was at m/z 209. The diagnostic fragments, which gave some structural informations, were observed at m/z 134 and 161. These ions suggested that ring B and propane-unit of one unit are not involved in the linkage. Two ring A fragments at m/z 181 and 195 gave some clue to the nature of the other unit. These fragments suggested that other unit was not linked through either ring A or C_α.

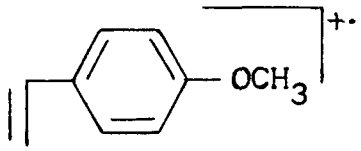
It can be said, on the basis of available data, that the compound is probably a dihydrobichalcone whose chalcone unit is linked through ring A to either C_β or ring B of dihydrochalcone unit.

Partial characterization of compound (XL)

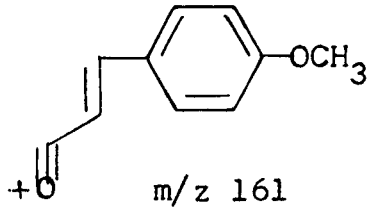
The compound melting at 183-6°C gave positive ferric chloride test and red colour with conc. H_2SO_4. Its i.r. spectrum exhibited hydroxyl stretching band at 3400 cm^{-1}, while the carbonyl band was observed at 1620 cm^{-1} indicative of hydrogen bonding between phenolic and carbonyl functionalities. The u.v. spectrum of this compound was almost identical to that of [I-3,II-3']-dihydrobichalcone (XXXVII) and displayed maxima at 275 and 350 nm. The ion with the highest mass to charge ratio, in the mass spectrum, was observed at m/z 449 (1.51%) while the base peak was at m/z 142. The mass spectrum showed peaks at 121, 134 and 161 which gave an idea that atleast one unit is a chalcone and that it is linked through ring A to other unit.



m/z 121

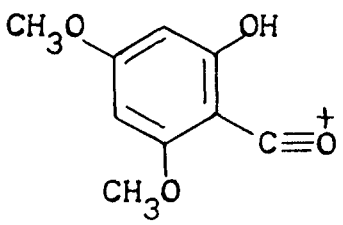


m/z 134

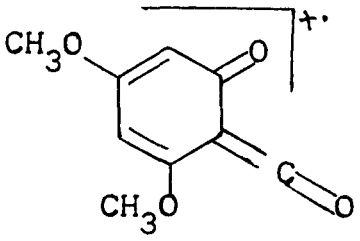


m/z 161

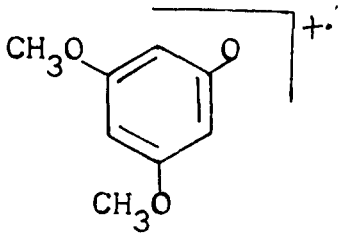
The fragments at m/z 152, 180 and 181 can be expected to be derived from the ring A of the other unit and confirmed the non-involvement of ring A in the linkage.



m/z 181



m/z 180

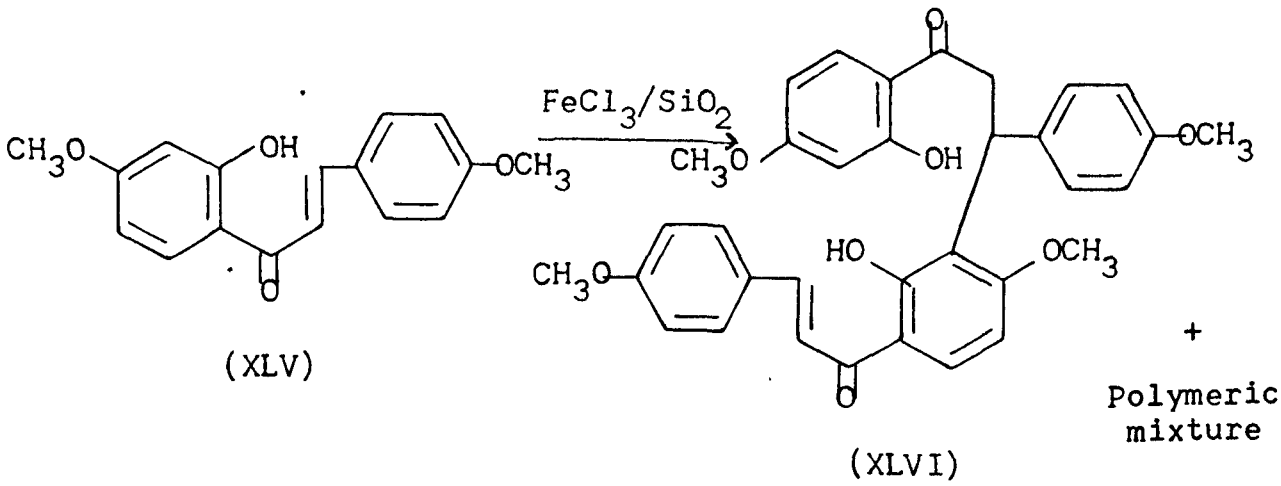


m/z 152

It is not possible to fully characterize the compound on the basis of available data. However, it can be said that the compound is a dihydrobichalcone. The ring A of the chalcone unit is involved in the linkage, while the dihydrochalcone unit is linked through either ring B or C_3-unit.

Reaction of 2'-hydroxy-4,4'-dimethoxychalcone (XLV) with silica bound ferric chloride

The reaction was performed as described in the preceding experiment. Thus, a solution of 2'-hydroxy-4,4'-dimethoxychalcone (XLV) in dichloromethane was added to the silica bound ferric chloride and the solvent was evaporated on a rotary evaporator under reduced pressure. The reaction mixture was stirred at room temperature for eight hours. The usual work up of the reaction afforded a brown gummy mass which was chromatographed over silica gel. Unreacted starting chalcone was obtained when the column was run using petrol:benzene (4:1) as the eluent. Elution of the column with petrol:benzene (1:1) yielded a bright yellow compound which was characterized as I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4'-tetramethoxy-[I-β,II-3']-dihydrobichalcone (XLVI) by its i.r., u.v., n.m.r. and mass spectra. Further elution of the column with more polar solvents such as ethyl acetate and methanol furnished a complex mixture of polymeric products which could not be purified even on repeated column chromatography.



(XLV)

(XLVI)

Characterization of I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4'-tetramethoxy-[I-β,II-3']-dihydrobichalcone (XLVI)

The product melting at 173-4°C gave positive alcoholic ferric chloride test and red colour with conc. H_2SO_4 indicating the presence of chalcone moiety. The presence of hydroxy group was further confirmed by its infra-red spectrum. I.r. spectrum exhibited the hydroxyl band at 3430 cm^{-1}, while the band at 1630 cm^{-1} was due to the carbonyl group. Its ultra-violet spectrum proved very helpful in the structure elucidation. It showed maxima at 240, 275, 330 and 370 nm. The band at 370 nm confirmed the presence of chalcone moiety in the compound. The molecular ion peak, expected at m/z 568, was not observed in the mass spectrum, however, the peaks corresponding to $(M+1)^+$ and $(M+2)^{+\cdot}$ ions at m/z 569 and 570, respectively, were intense (Fig.21). The possibility of a tetrahydrobichalcone was ruled out, since the band at 370 nm, in the u.v. spectrum, clearly indicated the presence of chalcone unit. The structure of this compound was elucidated with the help of its n.m.r. and mass spectra.

N.m.r. spectrum (Fig.22) of this compound exhibited two downfield singlets at δ 13.35 and 12.69. These signals were assigned to the two phenolic protons. Three singlets at δ 3.79, 3.81 and 3.86, integrating for three, six and three protons, respectively, were ascribed to the four methoxy groups. The aromatic region of the spectrum integrated for fifteen protons. The possibi-

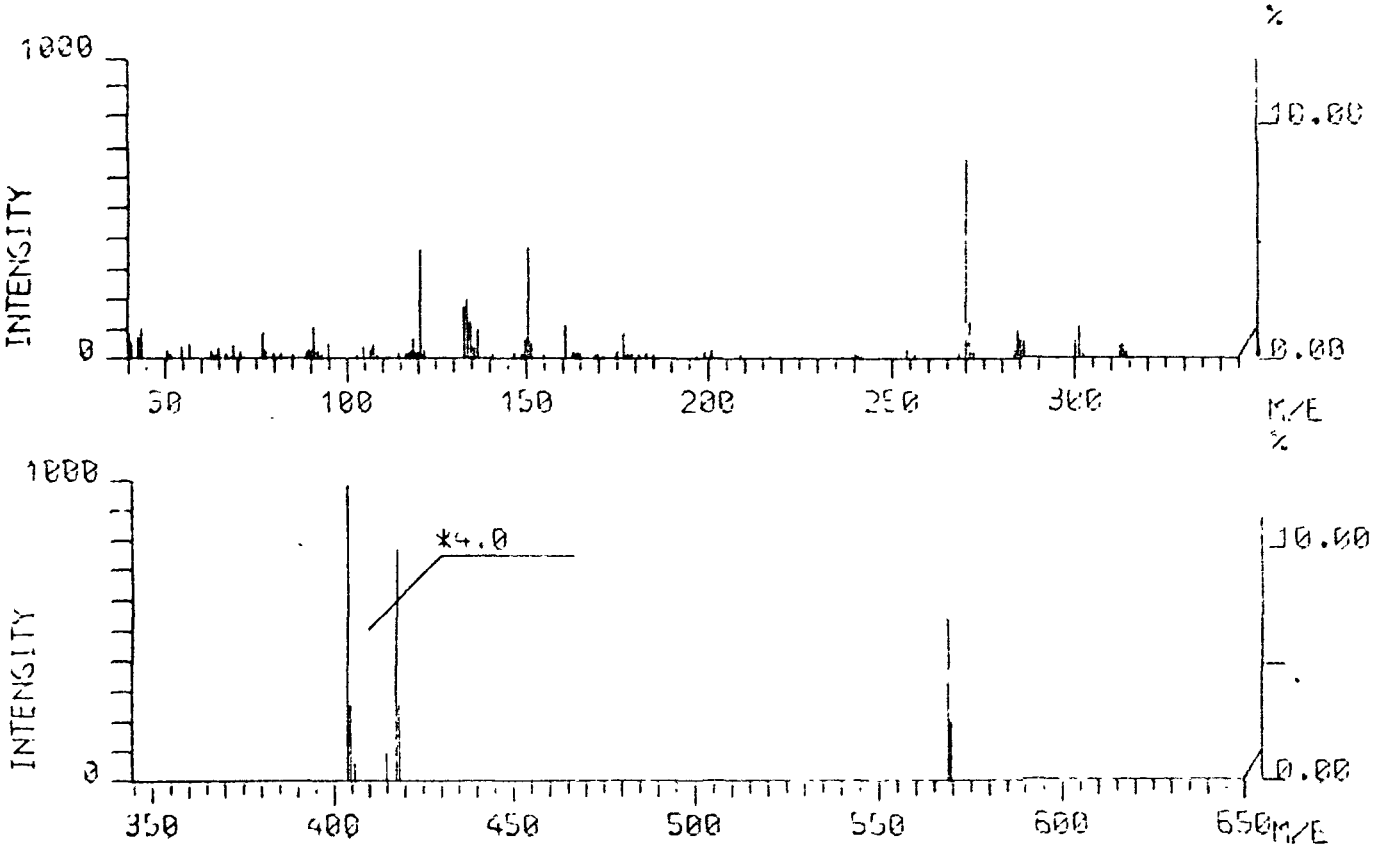

%
1000
INTENSITY
10.00
0
0.00
50
100
150
200
250
300
M/E
%
1000
*4.0
INTENSITY
10.00
0
0.00
350
400
450
500
550
600
650M/E

Fig. 21

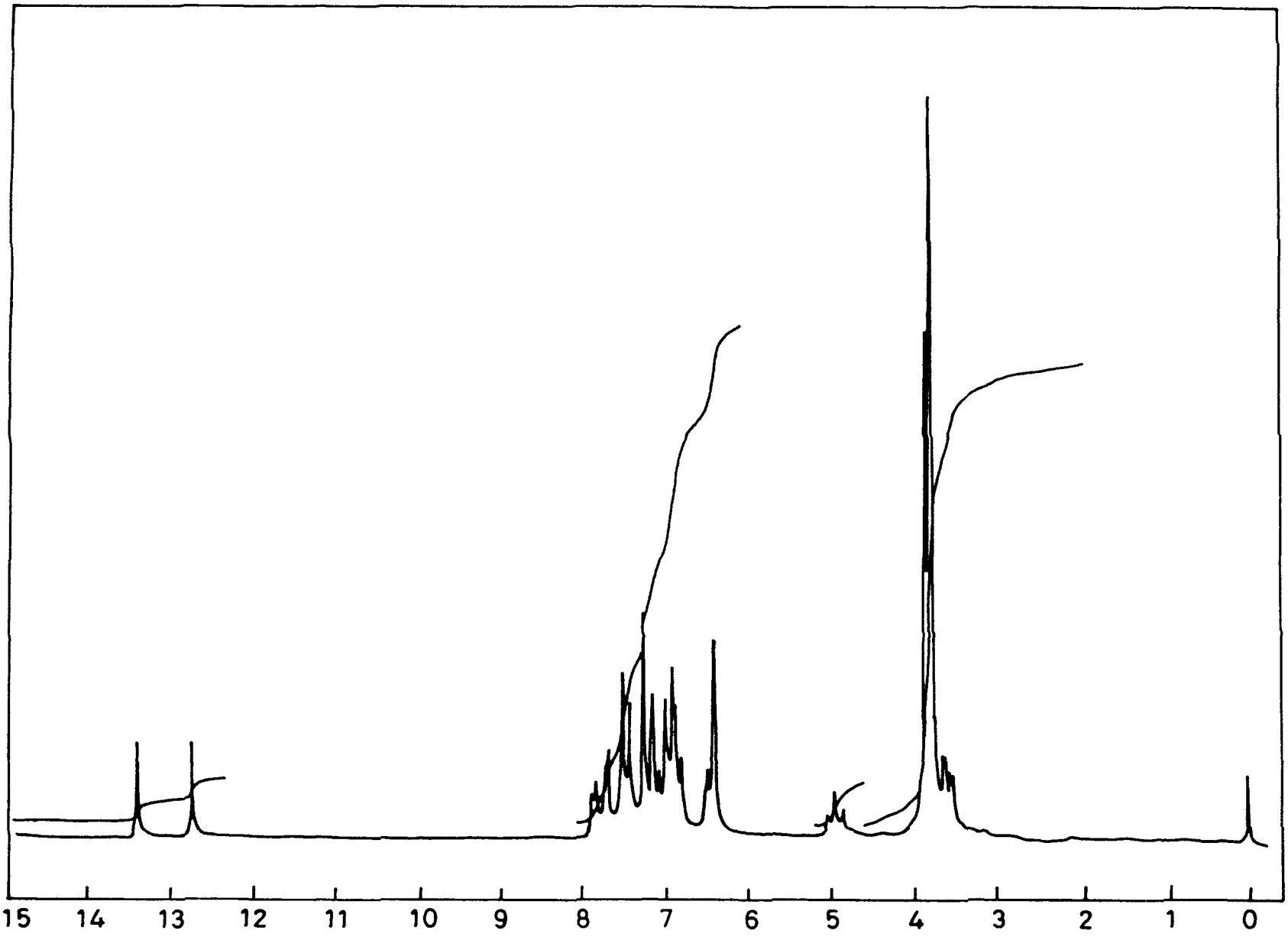
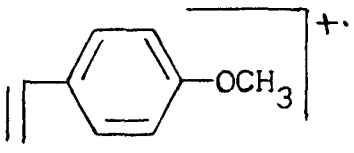


FIG. 22

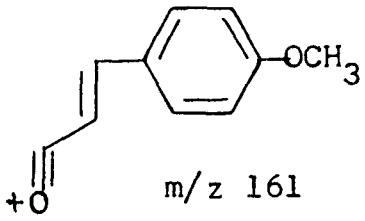
lity of a tetrahydrobichalcone was, therefore, eliminated. The aromatic region displayed two pairs of A_2B_2 doublets (J=9 Hz) attributable to the protons on B rings of the dihydrochalcone and chalcone moieties. The doublets of two protons each appearing at ð 6.84 and 7.20 were assigned to I-3,5-H and I-2,6-H, respectively, while the doublets of two protons each at ð 6.92 and 7.46 were assigned to II-3,5-H and II-2,6-H, respectively. It became clear that neither of the B rings was involved in the linkage. A shielded multiplet, in the aromatic region, centred at ð 6.45 integrating for three protons could only be attributed to the protons on the electron rich rings A. Two more downfield doublets (J=9 Hz), each for one proton at ð 7.73 and 7.78 were ascribed to the I-6' and II-6' protons, respectively. Since the protons on the C-6' carbons appeared as ortho-coupled doublets, the multiplet centred at ð 6.45 was attributed to the protons on the I-3',5' and II-5' carbons. The olefinic protons of the chalcone unit were seen as two doublets (J=15 Hz) at ð 7.18 and 7.67 imputed to the C_α and C_β protons, respectively. It can be concluded that the chalcone unit is linked to the other unit through C-3'. The nature and the point of linkage of the other unit was easily established on the basis of chemical shifts of the protons on the C-3 unit of the dihydrochalcone moiety. A partially superimposed multiplet centred at ð 3.58 and a triplet centred at ð 4.90 (J=8 Hz) for two and one protons, respectively, could only be attributed to methylene and methine protons of the dihydrochalcone unit. The signals at

∂ 3.58 and 4.90 were assigned to the protons on the α and β carbons, respectively. The chemical shift data of compound, XLVI, is shown in table II. The compound was, thus, characterized as I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4'-tetramethoxy-[I-β,II-3']-dihydrobichalcone (XLVI). The other possible assignment, [I-α,II-3']-dihydrobichalcone was eliminated in the light of plausible mechanism of the reaction. However, further distinction between the possible isomers was not possible with the existing facilities.

The structural assignment is further supported by its mass spectrum (Chart III). The molecular ion at m/z 568 was not present in the spectrum, however, the peaks at m/z 569 (14.02) and 570 (5.39), corresponding to M+1 and M+2 ions, were present. It can be said that the molecule is highly susceptible to hydrogen abstraction and that was, probably, why many ions were observed with one more mass unit. The presence of chalcone unit was indicated by the fragments at m/z 134 and 161. These ions confirmed the non-involvement of ring B and C_3-unit of the chalcone in the linkage.



m/z 134



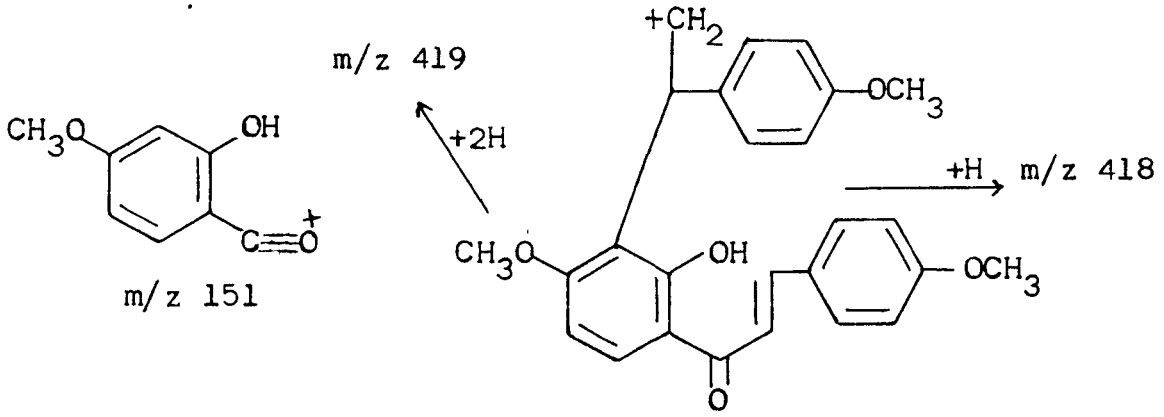
m/z 161

Table-II: Chemical shifts of protons of I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4'-tetramethoxy-[I-β-II-3']-dihydrobichalcone (XLVI).

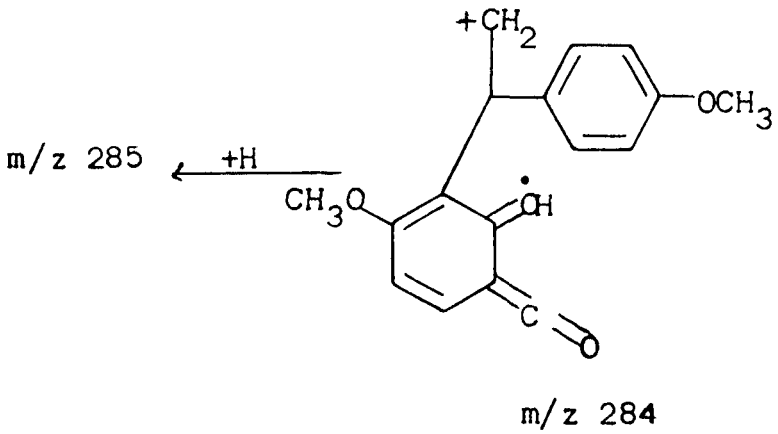
Proton assignment	Chemical shifts (δ ppm)
H-I-α	3.58 (mc, 2H)
MeO-I-4	3.79 (s, 3H)
MeO-I-4',II-4	3.81 (s, 6H)
MeO-II-4'	3.86 (s, 3H)
H-I-β	4.90 (t, J=8 Hz, 1H)
H-I-3',5',II-5'	6.45 (mc, 3H)
H-I-3,5	6.84 (d, J=9 Hz, 2H)
H-II-3,5	6.92 (d, J=9 Hz, 2H)
H-II-α	7.18 (d, J=15 Hz, 1H)
H-I-2,6	7.20 (d, J=9 Hz, 2H)
H-II-2,6	7.46 (d, J=9 Hz, 2H)
H-II-β	7.67 (d, J=15 Hz, 1H)
H-I-6'	7.73 (d, J=9 Hz, 1H)
H-II-6'	7.78 (d, J=9 Hz, 1H)
HO-I-2'	12.69 (s, 1H)
HO-II-2'	13.35 (s, 1H)

s= singlet, d= doublet, t= triplet, mc= multiplet centred at; Spectrum run in $CDCl_3$ at 80 MHz and TMS as internal standard δ= 0.00.

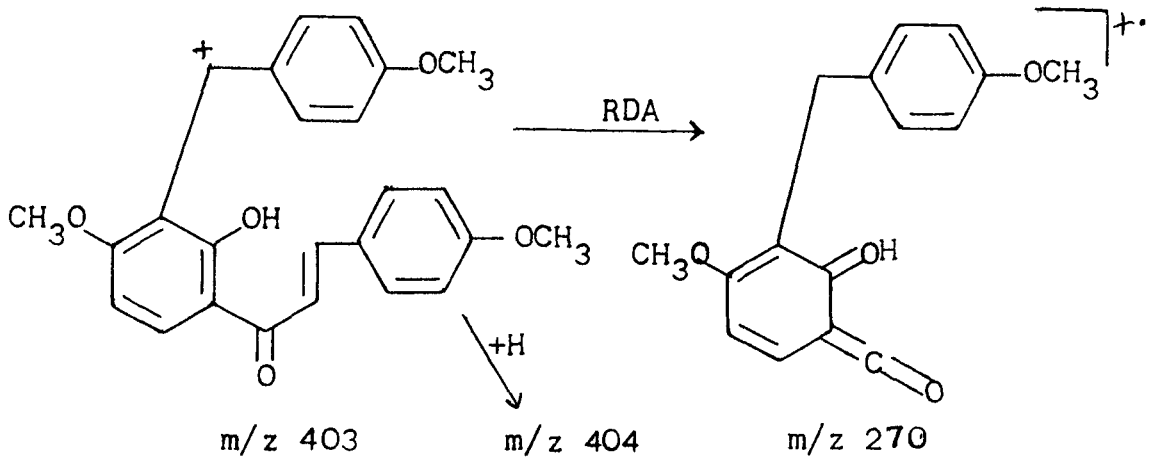
The fragment at m/z 151, due to the benzoyl cation, can only be derived from the dihydrochalcone unit. This confirmed the linkage of the dihydrochalcone unit through either C_3-unit or ring B. An ion at m/z 417 can be expected from the molecular ion by the loss of benzoyl radical, however the peaks were at m/z 418 and 419.



The peak at m/z 284 can be attributed to either the doubly charged molecular ion or to the fragment formed by the RDA fragmentation of the chalcone unit of the ion appearing at m/z 418. The peak at m/z 285 may be due to the doubly charged $(M+2)^{++}$ ion, or it is quite probable that the peak at m/z 285 may be due to (284+H) ion.



The most structurally significant peaks in the spectrum were at m/z 404 (100%) and 270 (67.58%). The fission of the C_α-C_β bond in dihydrochalcone unit of the molecular ion gave a fragment at m/z 403 recorded as (403+H) ion. RDA fragmentation of this ion provided another diagnostic fragment at m/z 270.



The ions at m/z 404 and 270 can only be obtained if the linkage of the dihydrochalcone unit is through β carbon. Thus, the structure of the compound was further confirmed as I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4'-tetramethoxy-[I-β,II-3']-dihydrobichalcone (XLVI).

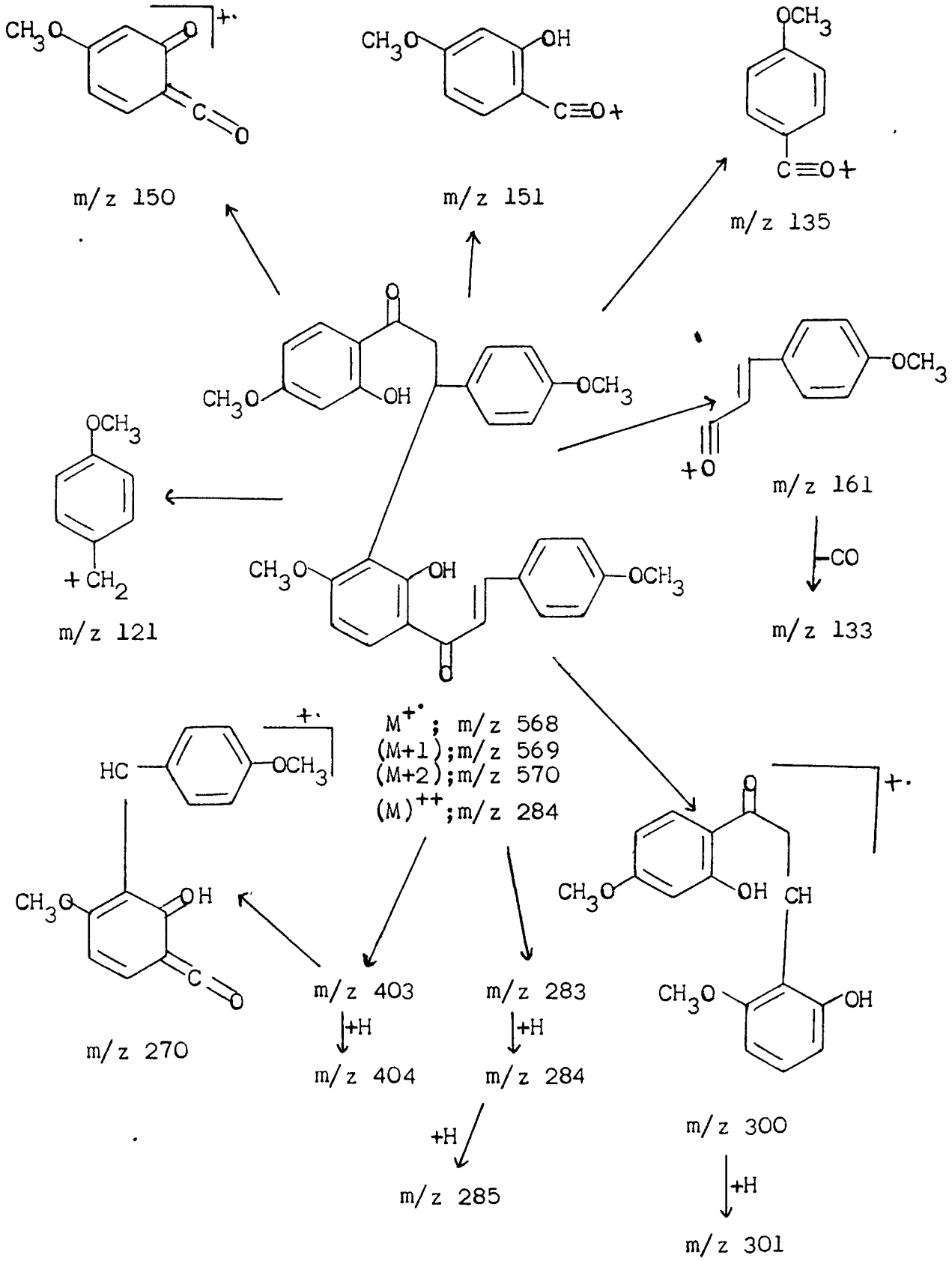
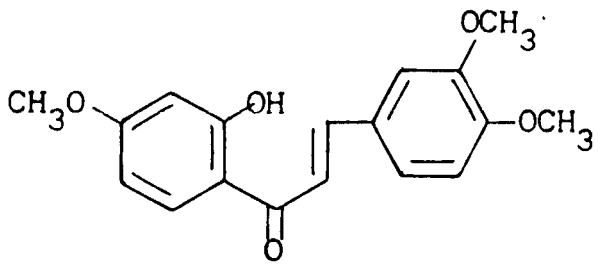

m/z 150
m/z 151
m/z 135
m/z 161
CO
m/z 133
m/z 121
M+· ; m/z 568
(M+1);m/z 569
(M+2);m/z 570
(M)++;m/z 284
m/z 270
m/z 403
+H
m/z 404
m/z 283
+H
m/z 284
+H
m/z 285
m/z 300
+H
m/z 301

Chart III

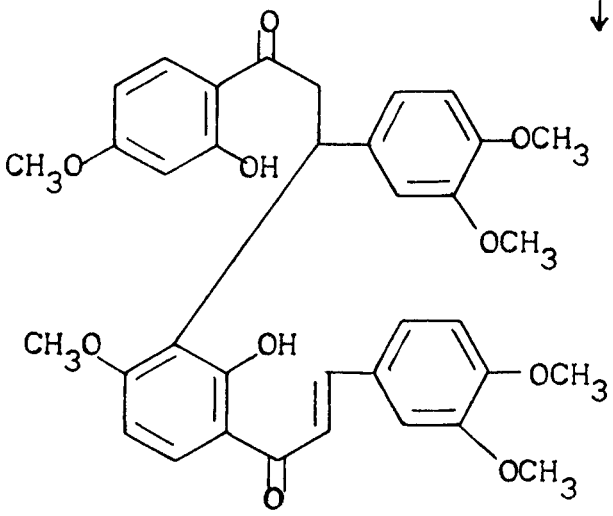
Reaction of 2'-hydroxy-3,4,4'-trimethoxychalcone (XLVII) with silica bound ferric chloride

The reaction of 2'-hydroxy-3,4,4'-trimethoxychalcone with silica bound ferric chloride was performed in the previously described manner. Thus, chalcone (XLVII) was dissolved in dichloromethane and added to the silica bound ferric chloride. The solvent was evaporated under reduced pressure and the resulting mixture left stirring at room temperature for six hours. The reaction was worked up in the usual manner to give a crude gummy mass which was subjected to column chromatography. Elution with petrol:benzene (1:1) afforded unreacted 2'-hydroxy-3,4,4'-trimethoxychalcone. Further elution of the column with benzene yielded a yellow compound which was characterized as I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4, I-4',II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII). Furthermore elution with the same solvent provided another yellow product, characterized as I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4, I-4',II-4'-hexamethoxy-[I-β,II-5']-dihydrobichalcone (XLIX). Major amount of polymeric products was obtained when column was eluted with ethyl acetate and acetone.



(XLVII)

$FeCl_3/SiO_2$

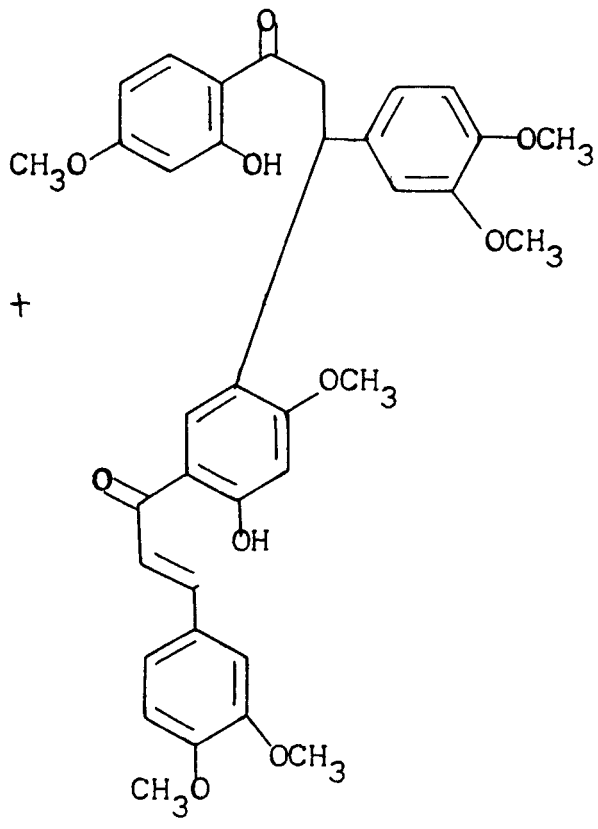


(XLVIII)

+

Polymeric mixture

+



(XLIX)

Characterization of I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4', II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII)

The compound melting at 155-6°C gave positive alcoholic ferric chloride test and dark red colour with conc. H_2SO_4. The hydroxyl absorption band was observed, in the i.r. spectrum, at 3430 cm^{-1}, while the band at 1630 cm^{-1} was characteristic of hydrogen bonded carbonyl stretching. The mass spectrum exhibited the ion with highest mass to charge ratio at m/z 630 (Fig.23). It can be said that the compound is a dimeric product and that neither of the unit is cyclized. Its ultra-violet spectrum exhibited absorption maxima at 272, 314 and 375 nm. The presence of a chalcone unit was indicated by the band at 375 nm. The nature of the other unit and the points of linkage were established with the help of its n.m.r. (Fig.24) and mass spectra.

The most diagnostic peaks in the mass spectrum were at m/z 150, 151, 163, 164 and 191. The ion at m/z 191 clearly suggested that one unit was chalcone and that it was linked through ring A to the other unit. The peaks at m/z 163 and 164 also supported it. The ring A fragments at m/z 150 and 151 can only arise from the other unit if the non-involvement of ring A in the linkage be assumed. It can be said, on the basis of these data that the compound is a dihydrobichalcone and the chalcone unit is linked through ring A to either ring B or C_3-unit of the dihydrochalcone moiety.

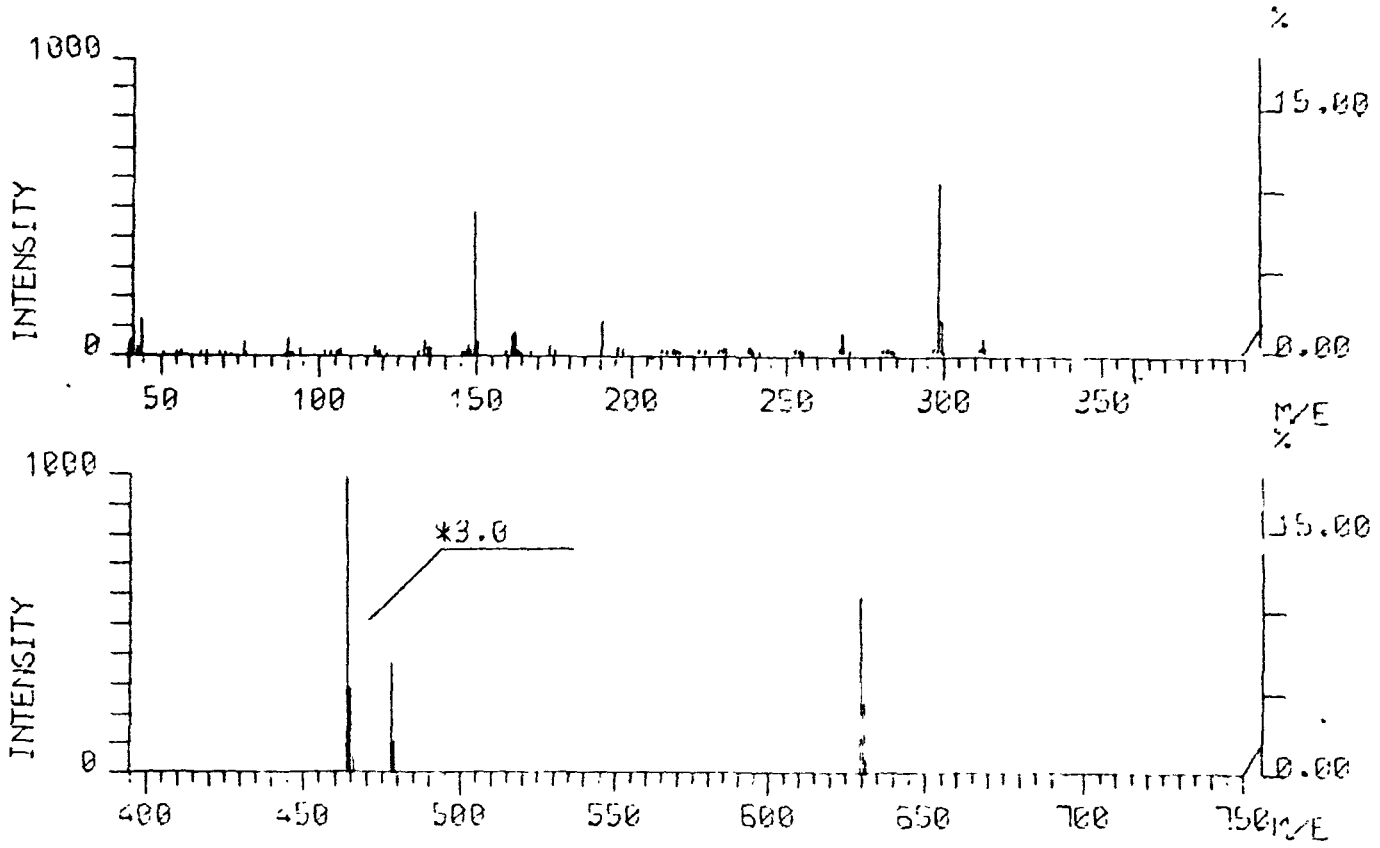

1000
INTENSITY
0
%
15.00
0.00
50
100
150
200
250
300
350
M/E
%
1000
INTENSITY
0
*3.0
15.00
0.00
400
450
500
550
600
650
700
750
M/E

Fig. 23

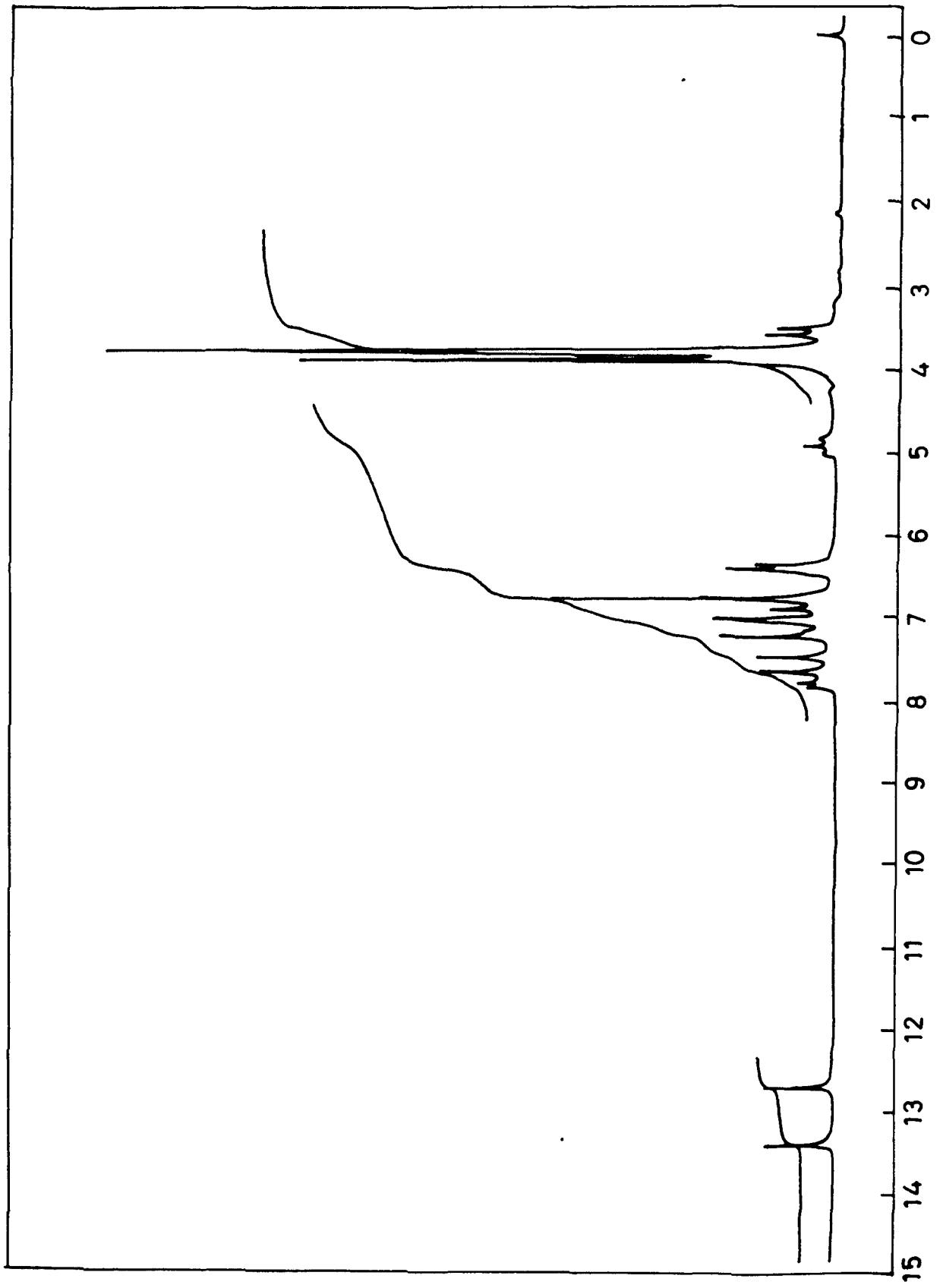
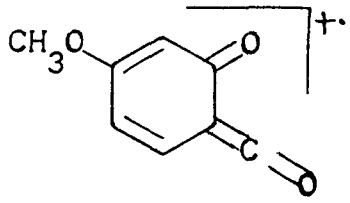
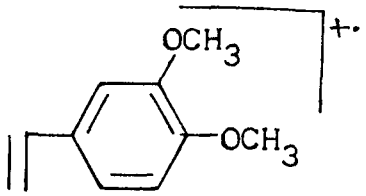


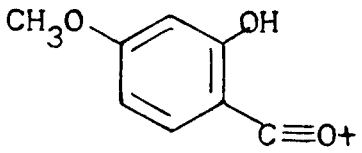
FIG. 24



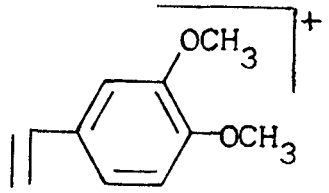
m/z 150



m/z 164



m/z 151



m/z 163

In the n.m.r. spectrum, signals for the six methoxy groups were observed as a compact group of singlets in the region ð 3.82-3.93. Two downfield singlets at ð 12.69 and 13.39, each for one proton were due to the two phenolic protons. At the lowest field in the aromatic region of the spectrum was seen a doublet (J=9 Hz) at ð 7.73 for two protons which was ascribed to the protons on the C-6' of the two units. A shielded multiplet centred at ð 6.44 for three protons was attributed to the protons on the I-3',5' and II-5' carbons of two A rings. These signals confirmed the involvement of one ring A in the interflavonoidic linkage. Signal for the ring B protons of the dihydrochalcone unit was observed as a singlet atð6.80 for three protons. A doublet at

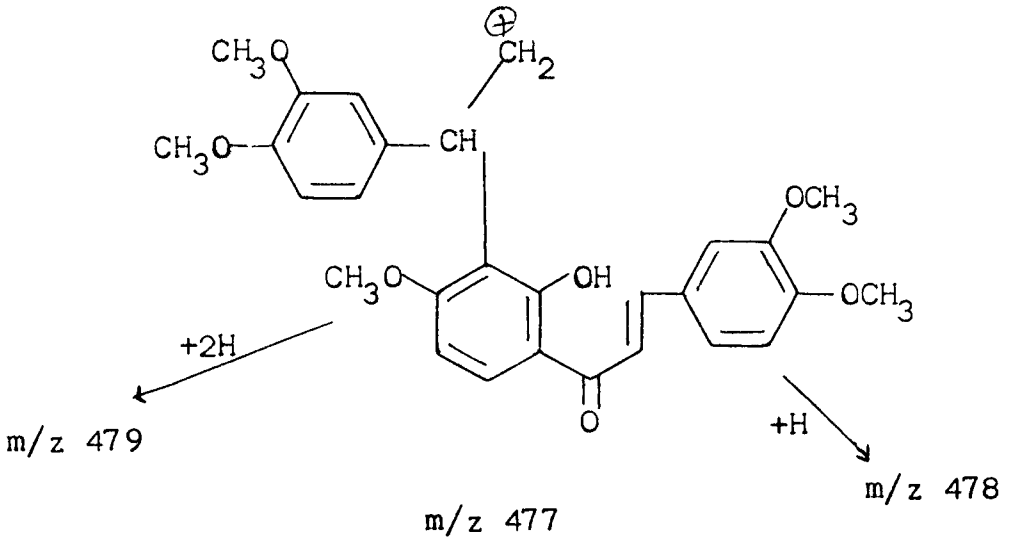
∂ 6.87 (J=9 Hz) for one proton was imputed to the proton on II-5 carbon. A multiplet centred at ∂ 7.13 for two protons was due to the II-2,6 protons. Signals for the olefinic protons of the chalcone unit were observed as a pair of doublets (J=15 Hz) at ∂ 7.37 and 7.77 assignable to C_α and C_β protons, respectively. A doublet for two protons at ∂ 3.57 (J=8 Hz) and a triplet at ∂ 4.95 (J=8 Hz) for one proton could only be assigned to the protons on the C_3-chain of the dihydrochalcone unit. The signal at ∂ 3.57 was attributed to α-methylene protons, while the triplet at ∂ 4.95 was assigned to the methine proton at β carbon. The chemical shifts of the protons of compound, XLVIII, are given in table III. The compound was, therefore, identified as I-2',II-2'-dihydroxy-I-3, II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII).

The establishment of the linkage was further supported by the mass spectrometry (Chart IV). The molecular ion peak at m/z 628 was not present, but peaks at m/z 629 and 630, corresponding to M+1 and M+2 ions, were present. The ion formed by the loss of benzoyl group from the molecular ion was not observed at m/z 477 but the peaks were present at m/z 478 and 479.

Table-III: Chemical shifts of protons of I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII).

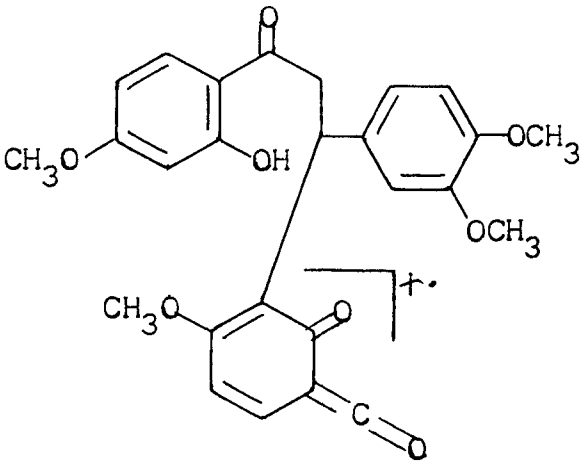
Proton assignment	Chemical shifts (∂ ppm)
H-I-α	3.57 (d, J=8 Hz, 2H)
MeO-I-3,II-3,I-4,II-4, I-4',II-4'	3.82-3.93 (merged singlets, 18H)
H-I-β	4.95 (t, J=8 Hz, 1H)
H-I-3',5',II-5'	6.44 (mc, 3H)
H-I-2,5,6	6.80 (s, 3H)
H-II-5	6.87 (d, J=9 Hz, 1H)
H-II-2,6	7.13 (mc, 2H)
H-II-α	7.37 (d, J=15 Hz, 1H)
H-I-6',II-6'	7.73 (d, J=9 Hz, 2H)
H-II-β	7.77 (d, J=15 Hz, 1H)
HO-I-2'	12.69 (s, 1H)
HO-II-2'	13.39 (s, 1H)

s= singlet, d= doublet, t= triplet, mc= multiplet centred at; Spectrum run in $CDCl_3$ at 80 MHz and TMS as internal standard ∂= 0.00.

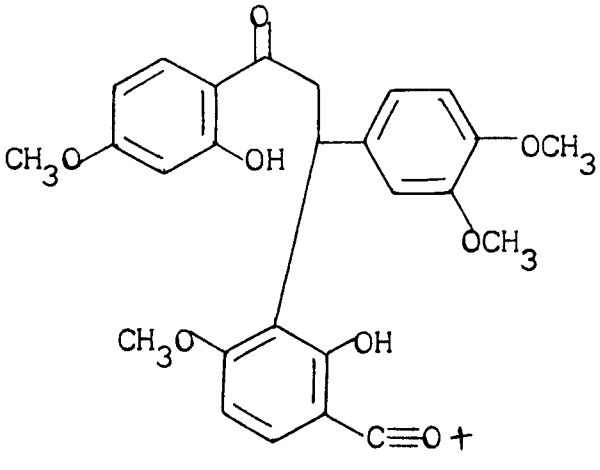


m/z 477

RDA fragmentation of the chalcone unit in the molecular ion afforded an ion at m/z 464 while the fission of the $-\overset{\overset{O}{\|}}{C}-C_{\alpha}$ bond gave an ion at m/z 465. The peak at m/z 464 was the base peak.

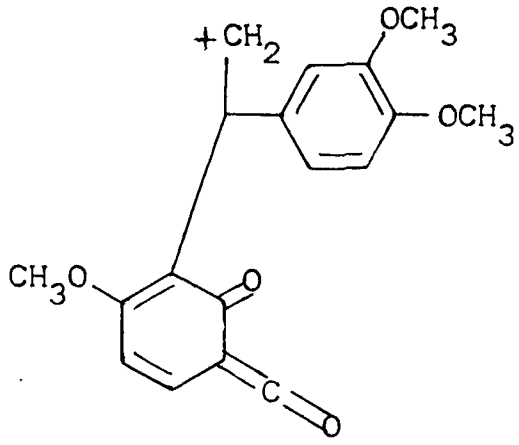


m/z 464

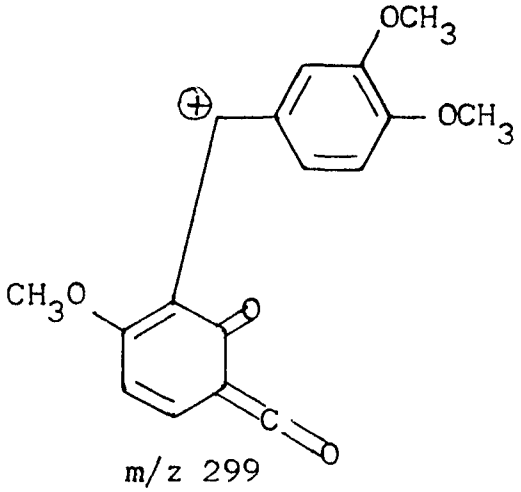


m/z 465

Another interesting peak in the spectrum was at m/z 313 which may be attributed to the ion formed by the loss of benzoyl radical from the fragment at m/z 464. The most diagnostic peak was seen at m/z 299. The formation of this ion can be explained by the fission of the C_α-C_β bond in the dihydrochalcone unit of fragment at m/z 464. These peaks can only be explained if the linkage be assumed as [I-β,II-3']. The possibility of the [I-α, II-3']-linkage was ruled out and the structure of this compound was confirmed as I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII).



m/z 313



m/z 299

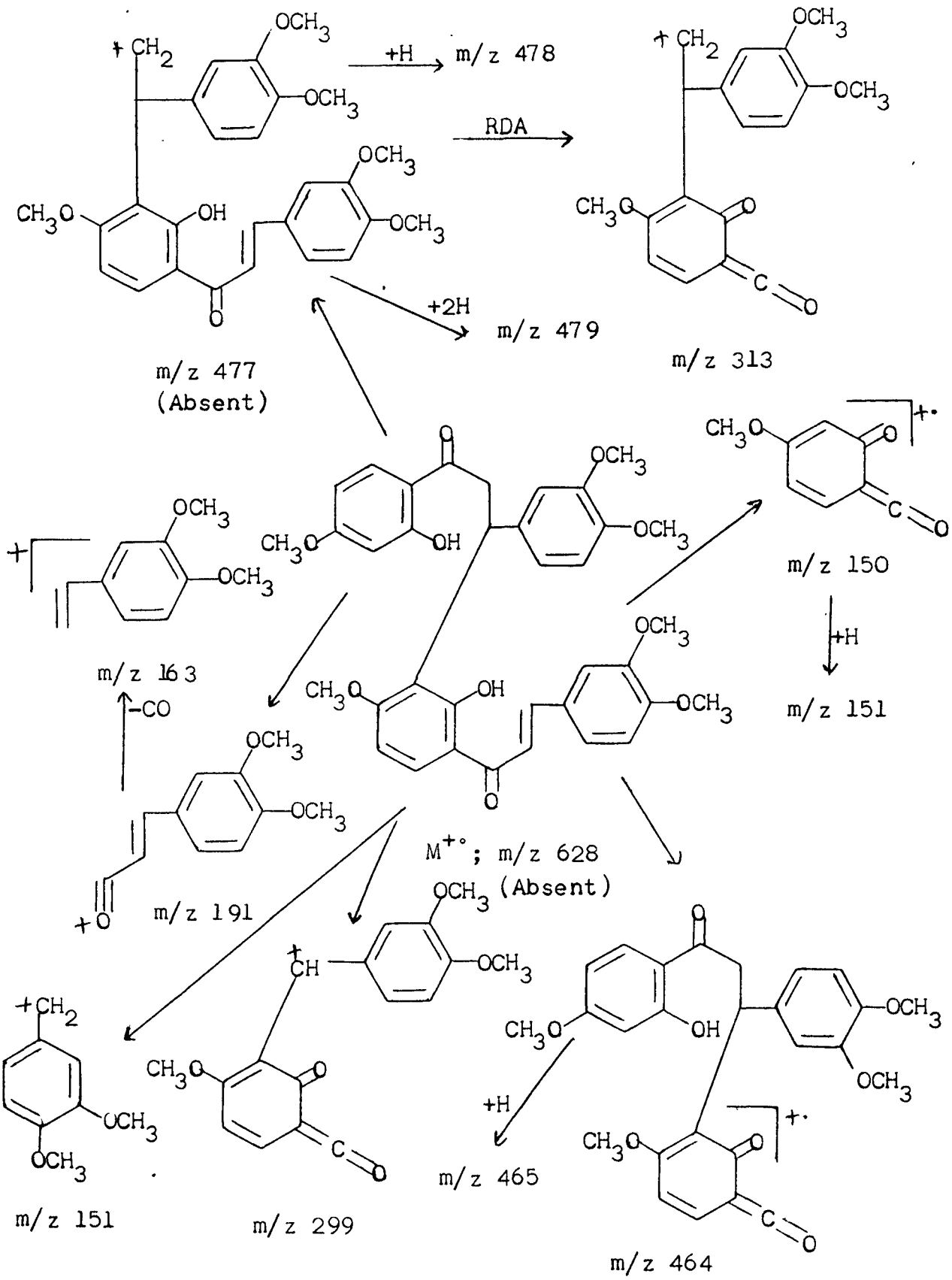

+H
m/z 478
RDA
+2H
m/z 479
m/z 313
m/z 477
(Absent)
m/z 150
m/z 163
-CO
m/z 151
m/z 191
M+°; m/z 628
(Absent)
m/z 151
m/z 299
m/z 465
m/z 464

Chart IV

Characterization of I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4', II-4'-hexamethoxy-[I-β,II-5']-dihydrobichalcone (XLIX)

This compound, m.p.174-5°C, also gave positive alcoholic ferric chloride test and red colour with conc. H_2SO_4. It exhibited, in the i.r. spectrum, the absorption bands at 1622 and 3440 cm^{-1} which were corresponding to the hydrogen bonded carbonyl and hydroxy groups. Its ultra-violet spectrum exhibited the characteristic chalcone band II at 375 nm besides the bands at 270 and 320 nm. The mass spectrum (Fig.25) like that of previous one showed the peak at m/z 630 which was corresponding to M+2 ion. The molecular ion peak at m/z 628, however, could not be observed. The structure of this compound was established with the help of n.m.r. and mass spectra.

Its mass spectrum contained some very useful peaks in locating the position of linkage. These peaks at m/z 150, 151, 164 and 191 gave much information on the nature of this compound. RDA fragment at m/z 164 alongwith the 3,4-dimethoxycinnamoyl cation peak at m/z 191 clearly indicated the presence of a chalcone moiety and also the involvement of ring A of the chalcone unit in the linkage. The peaks at m/z 150 and 151 could only be expected from the other unit and supported the non-involvement of the ring A of the dihydrochalcone unit in the linkage.

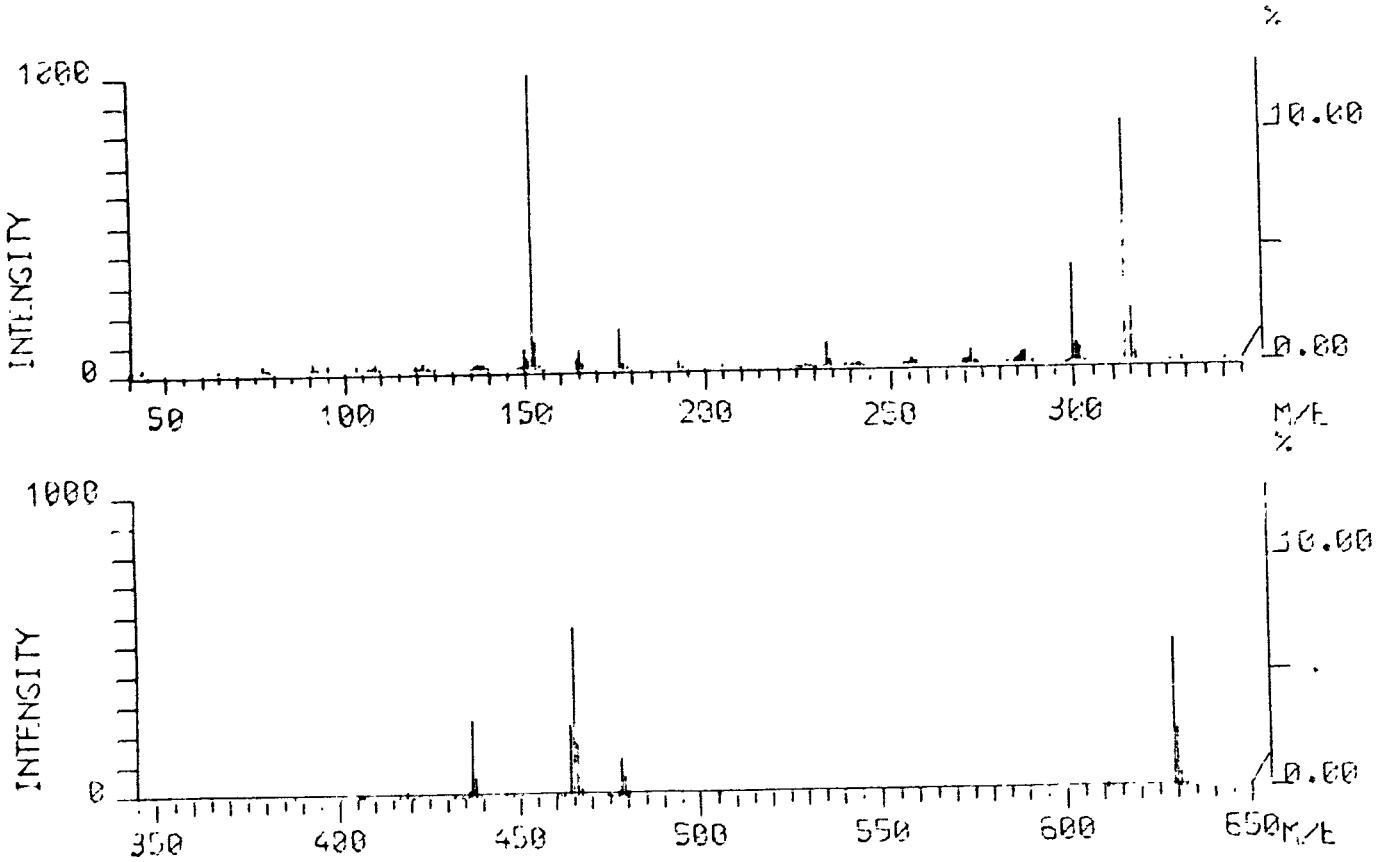
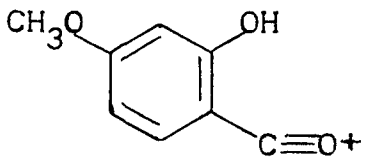
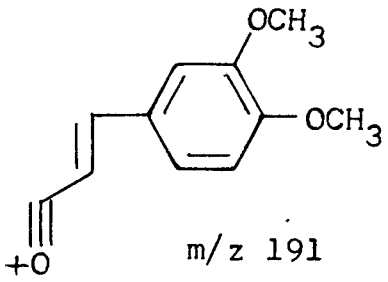

%
1000
INTENSITY
0
10.00
0.00
50
100
150
200
250
300
M/E
%
1000
INTENSITY
0
10.00
0.00
350
400
450
500
550
600
650M/E

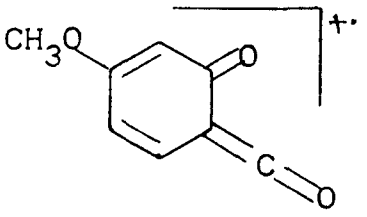
Fig. 25



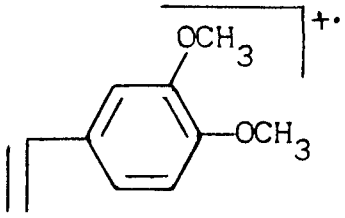
m/z 151



m/z 191



m/z 150



m/z 164

In the n.m.r. spectrum (Fig.26) was observed a group of merged signals in the region δ 3.81-3.94 which integrated for twenty protons. These signals were attributed to the six methoxyl protons and two methylene protons on the I-α carbon. A triplet at δ 5.38 (J=8 Hz) for one proton was ascribable to the methine proton on the C_β of dihydrochalcone unit. A multiplet centred at δ 6.43 for three protons could only be ascribed to the protons on the electron rich A rings of the two units. This signal was assigned to the protons on the I-3',5' and II-3' carbons. Two downfield signals in the aromatic region, a doublet at δ 7.81 (J=9 Hz) and a singlet at δ 7.86, each integrating for one proton, were ascribed to I-6' and II-6' protons, respectively. Since the signal for the proton on the II-6' carbon was observed as a singlet, the position

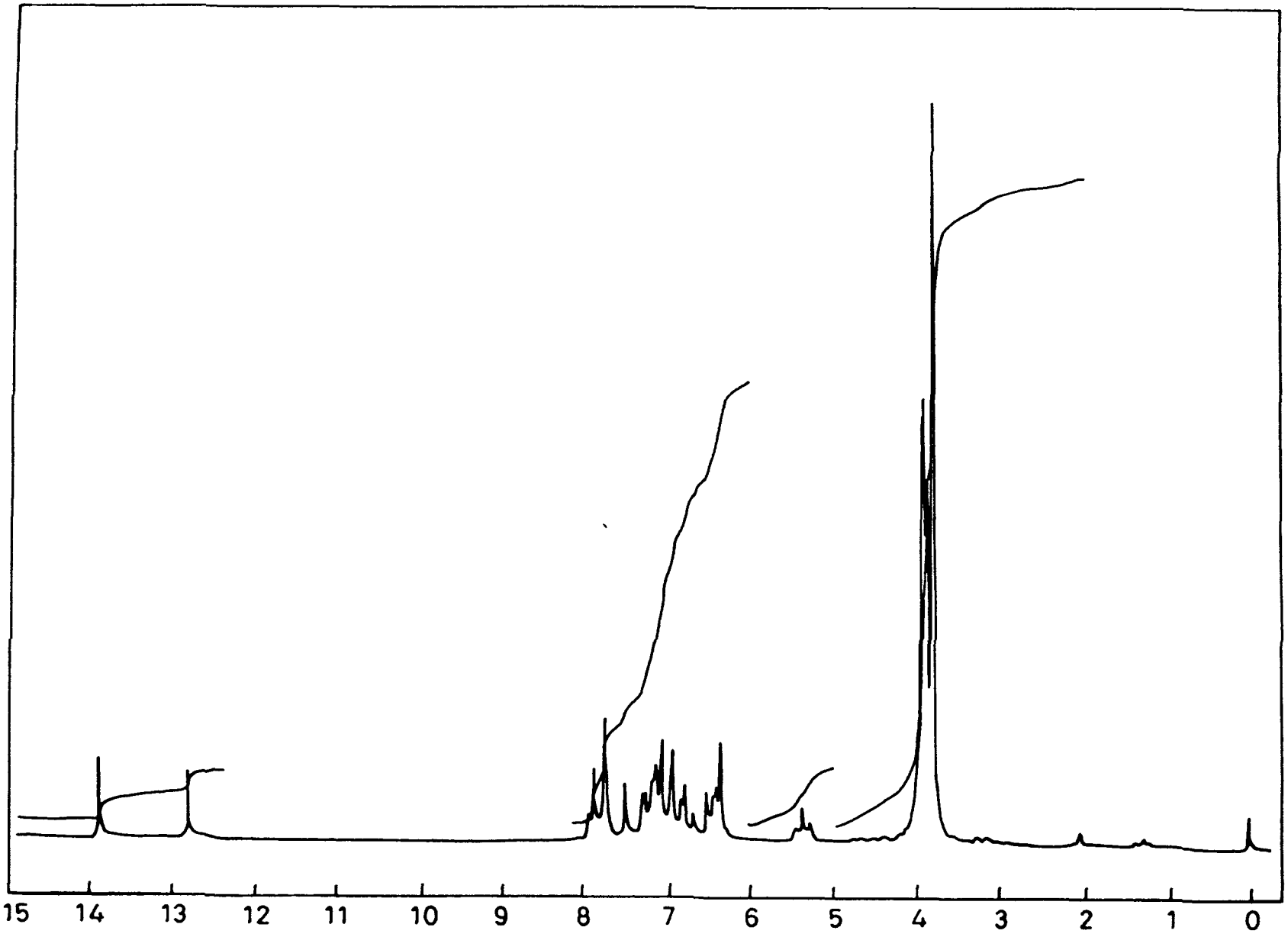
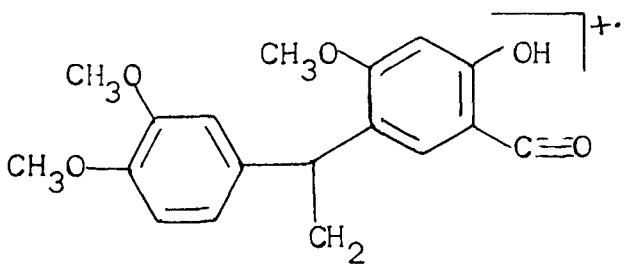


FIG. 26

of the linkage of chalcone unit was established at 5'-carbon. Two more doublets (J=9 Hz) at ∂ 6.77 and 6.90 each for one proton were imputed to the protons on the I-5 and II-5 carbons. A multiplet centred at ∂7.13 integrating for four protons was imputed to the remaining protons on the two B rings in the positions I-2,6 and II-2,6. Signals for two phenolic protons were observed as two singlets at ∂ 12.77 and 13.83. The chemical shift data of the compound, XLIX, is given in table IV.

The mass spectrum of the compound was very much alike to that of [I-β, II-3']-dihydrobichalcone (XLVIII). The fragmentation pattern of the compound, XLIX is shown in chart V. The mass spectrum contained the peaks at m/z 629 and 630 which were attributed to the (M+1) and (M+2) ions. The ion arising from the molecular ion by the loss of benzoyl group of the dihydrochalcone unit was observed at m/z 478. Usual RDA fragments were observed at m/z 464 and 465. Apeak at m/z 314 can be attributed to either the doubly charged molecular ion, M^{++} or to the fragment derived from the ion at m/z 465 by the loss of benzoyl group.



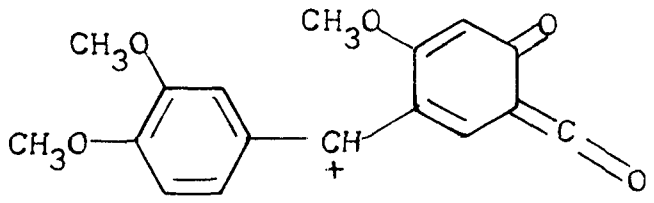
m/z 314

Table-IV: Chemical shifts of protons of I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-5']-dihydrobichalcone (XLIX).

Proton assignment	Chemical shifts (∂ ppm)
MeO-I-3,II-3,I-4,II-4, I-4',II-4' and H-I-α	3.81-3.94 (complex singlets, 20H)
H-I-β	5.38 (t, J=8 Hz, 1H)
H-I-3',5',II-3'	6.43 (mc, 3H)
H-I-5	6.77 (d, J=9 Hz, 1H)
H-II-5	6.90 (d, J=9 Hz, 1H)
H-I-2,6,II-2,6	7.13 (mc, 4H)
H-II-α	7.39 (d, J=15 Hz, 1H)
H-I-6'	7.81 (d, J=9 Hz, 1H)
H-II-β	7.83 (d, J=15 Hz, 1H)
H-II-6'	7.86 (s, 1H)
HO-I-2'	12.77 (s, 1H)
HO-II-2'	13.83 (s, 1H)

s= singlet, d= doublet, t= triplet, mc= multiplet centred at; Spectrum run in $CDCl_3$ at 80 MHz and TMS as internal standard ∂= 0.00.

The most structurally diagnostic fragment was at m/z 299 (37.51%). The loss of carbon monoxide from the fragment at m/z 314 might have given an ion at m/z 286 which was recorded as (286+H) ion The compound was therefore identified, on the basis of above data, as the I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexa-methoxy-[I-β,II-5']-dihydrobichalcone (XLIX).



m/z 299

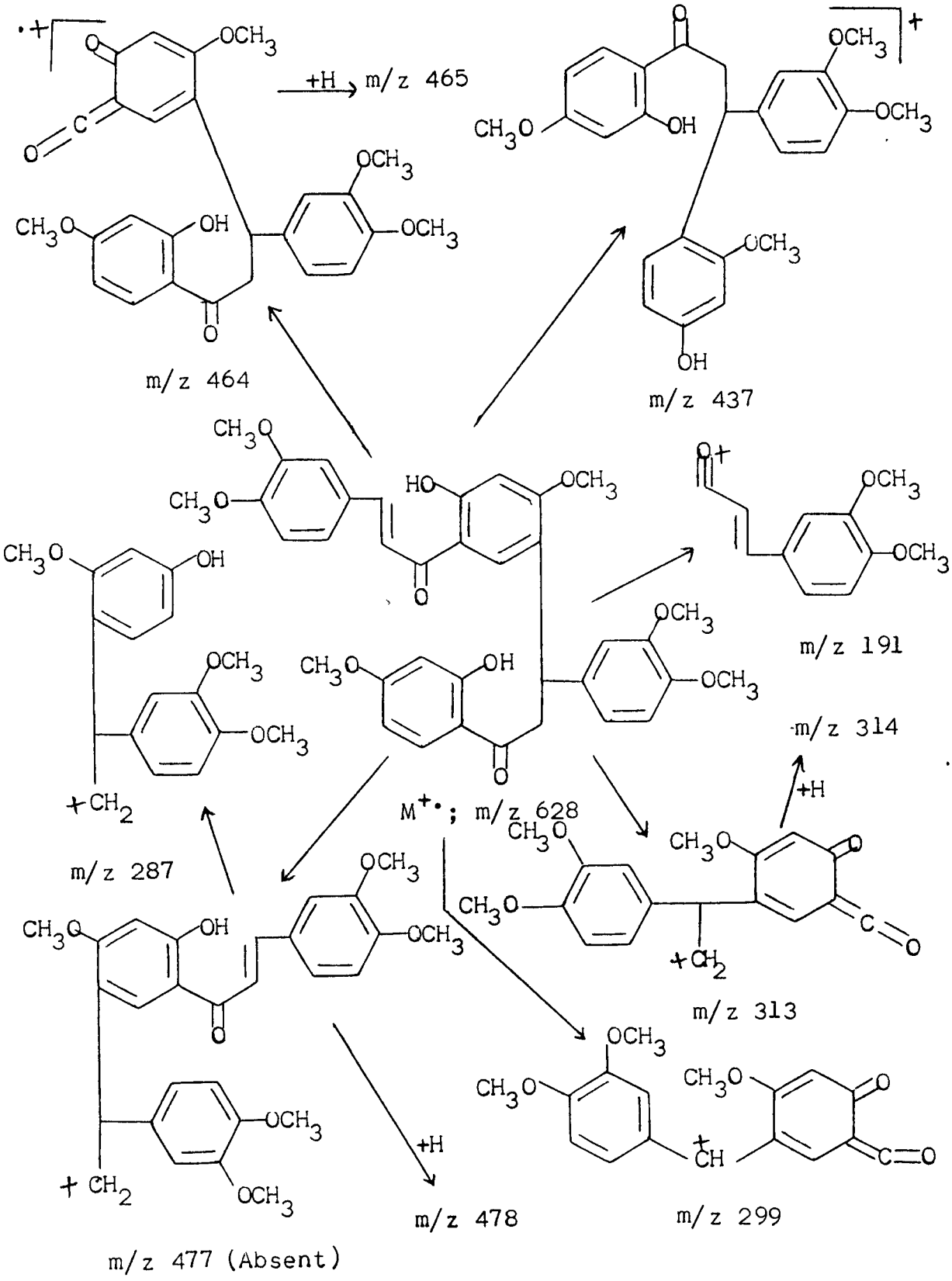
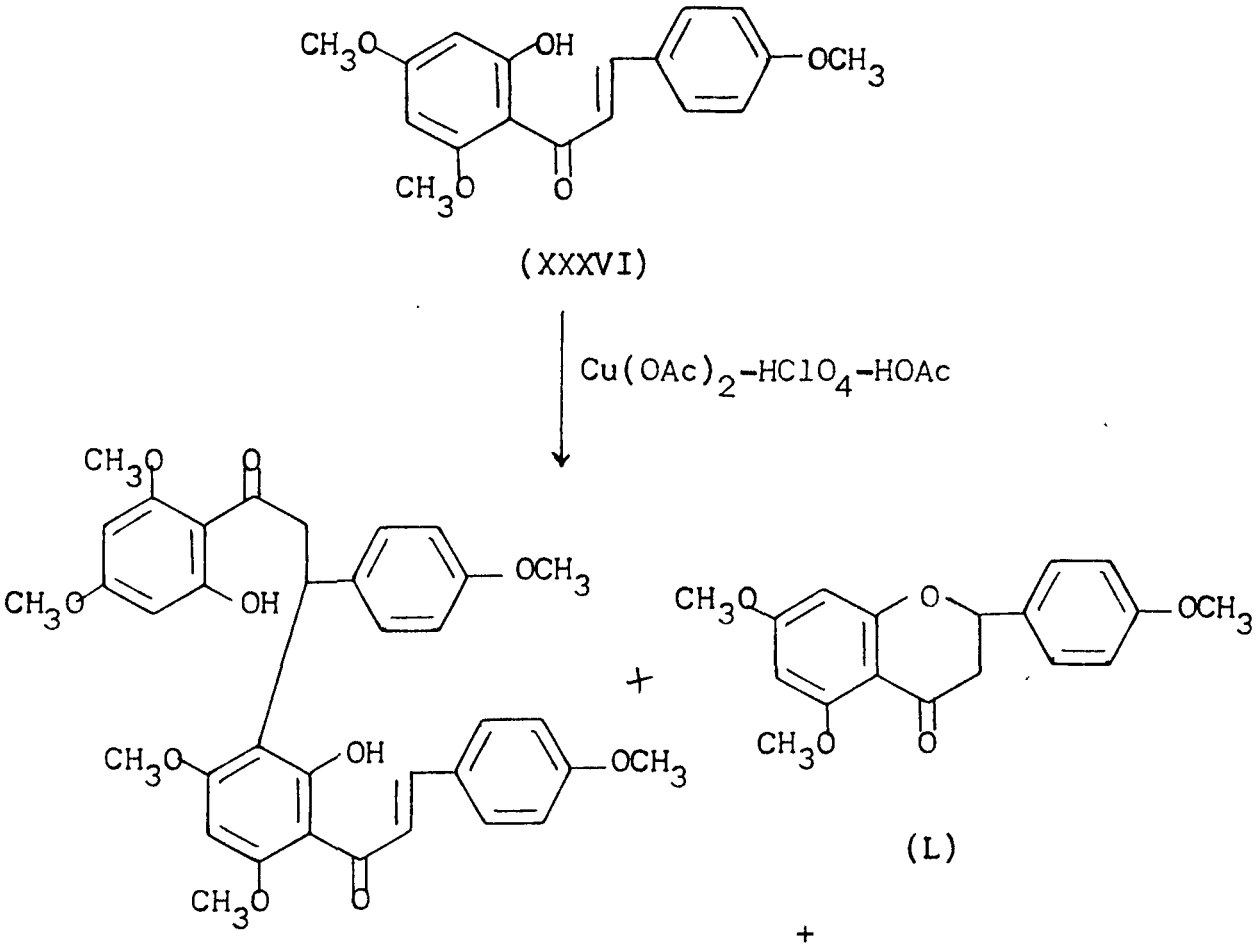

+H
m/z 465
m/z 464
m/z 437
m/z 191
m/z 314
M+•; m/z 628
m/z 287
m/z 313
m/z 478
m/z 299
m/z 477 (Absent)

Chart V

Reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI) with copper(II) acetate in the presence of perchloric acid

To a solution of copper(II) acetate in glacial acetic acid was added 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI) and perchloric acid. The reaction mixture was stirred at room temperature for 20 days. The contents were then poured into a dilute solution of sodium bicarbonate. The organic material was extracted with ethyl acetate. The ethyl acetate layer was washed, dried and evaporated to give a crude yellow solid which was subjected to column chromatography. Unreacted material was removed when the column was eluted with petrol:benzene (1:1). Further elution of the column with benzene:ethyl acetate (99:1) yielded a dark orange product which was found identical in all respects to an authentic sample of I-2',II-2'-dihydroxy-I-4,II-4, I-4',II-4',I-6',II-6'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XXXVII) (m.p., i.r., u.v., n.m.r. and mass spectra). A white compound was obtained when the benzene:ethyl acetate (19:1) was used as the eluent. This compound was characterized as 5,7,4'-trimethoxyflavanone (L). Finally, the column was eluted with ethyl acetate to yield a mixture of polymeric products.



(XXXVI)

(XXXVII)

(L)

Polymeric mixture

Characterization of 5,7,4'-trimethoxyflavanone (L)

The compound melting at 121-2°C showed, in its mass spectrum, the molecular ion peak at m/z 314. It gave negative alc. $FeCl_3$ test and pink colour with Mg-HCl[3c]. The absence of hydroxy group was confirmed with its i.r. spectrum which displayed carbonyl absorption band at 1660 cm^{-1}, characteristic of flavanone carbonyl. Its ultra-violet spectrum exhibited two characteristic flavanone bands[10] at 283 and 320 nm. The structure of the compound was elucidated with the help of n.m.r. and mass spectra.

Its n.m.r. spectrum displayed a singlet for nine protons at δ 3.80 assignable to three methoxyl protons. A multiplet centred at δ 2.84 for two protons and a doublet of doublet at δ 5.25 (J_{trans}=11 Hz, J_{cis}=5 Hz) for one proton were attributed to the C-3 and C-2 protons, respectively. Ring A protons were observed as a singlet for two protons at δ 6.00. A pair of doublets (J=9 Hz) at δ 6.80 and 7.30, each for two protons and showing the A_2B_2 pattern, were assignable to the protons on the p-substituted B ring in the positions 3',5' and 2',6', respectively. The chemical shifts of protons of the compound, L, are shown in table V.

The structure is supported by the mass spectrometry (Chart VI). The base peak in the mass spectrum was at m/z 134, a RDA fragment derived from ring B. Other ring B ions were present

Table-V: Chemical shifts of protons of 5,7,4'-trimethoxy-flavanone (L).

Proton assignment	Chemical shifts (∂ ppm)
H-3	2.84 (mc, 2H)
MeO-5,7,4'	3.80 (s, 9H)
H-2	5.25 (dd, J_{trans}=11 Hz, J_{cis}=5 Hz, 1H)
H-6,8	6.00 (s, 2H)
H-3',5'	6.80 (d, J=9 Hz, 2H)
H-2',6'	7.30 (d, J=9 Hz, 2H)

s= singlet, d= doublet, mc= multiplet centred at;
Spectrum run in $CDCl_3$ at 60 MHz and TMS as internal standard ∂= 0.00.

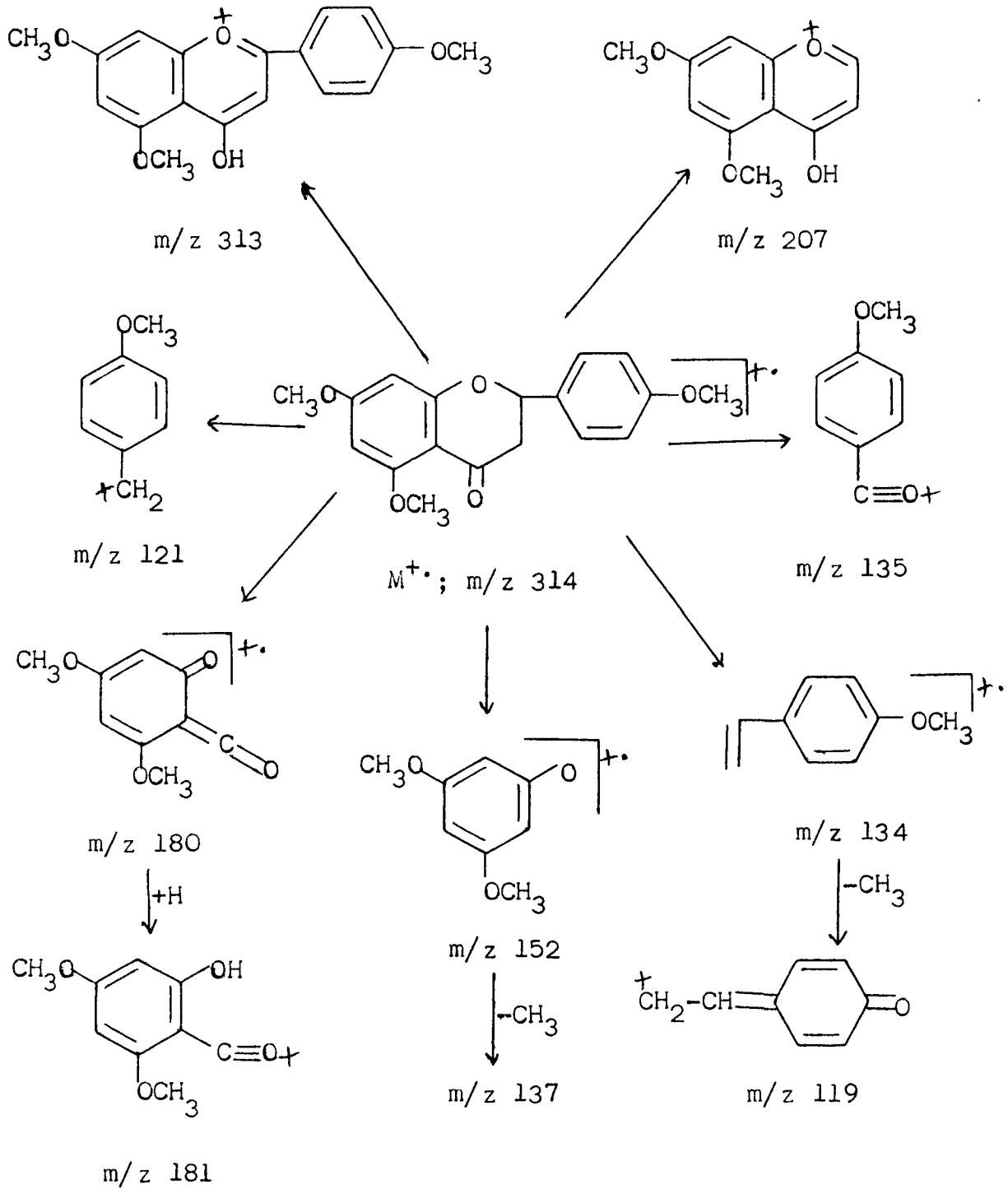
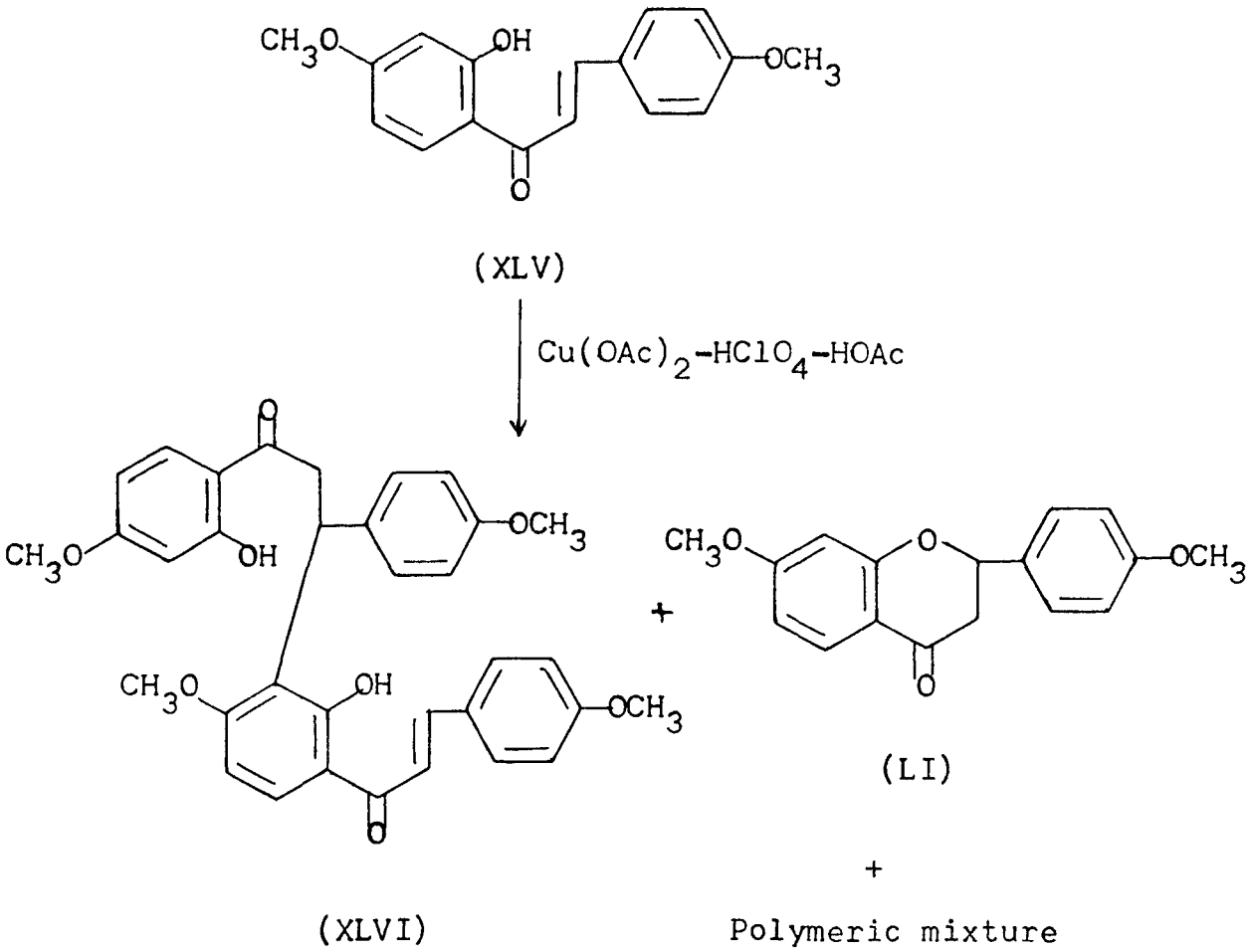

m/z 313
m/z 207
m/z 121
M+·; m/z 314
m/z 135
m/z 180
m/z 134
+H
m/z 152
-CH3
m/z 137
m/z 119
m/z 181

Chart VI

at m/z 135 and 121. Ring A fragments at m/z 180 and 181 were other RDA fragments. The fragment at m/z 152 was derived from the ion at m/z 180 by the loss of carbon monoxide. The loss of a hydrogen radical gave an ion at m/z 313, while the fragment at m/z 207 was formed by the loss of ring B from the molecular ion. The fragmentation pattern of the compound, L, is shown in chart VI. The compound was, therefore, identified as 5,7,4'-trimethoxyflavanone (L).

Reaction of 2'-hydroxy-4,4'-dimethoxychalcone (XLV) with copper(II) acetate in the presence of perchloric acid

The reaction of 2'-hydroxy-4,4'-dimethoxychalcone with copper(II) acetate was performed in the presence of perchloric acid in the previously described manner. Thus, a mixture of 2'-hydroxy-4,4'-dimethoxychalcone (XLV), copper(II) acetate and perchloric acid in acetic acid was stirred at room temperature for 10 days. The reaction did not reveal any change and the contents were heated on the water bath for eight hours. The reaction was worked up in the usual manner to give a crude solid which was chromatographed over silica gel. Elution with a mixture of petrol:benzene (3:2) yielded unreacted starting material. Two compounds were eluted with different solvent systems which were characterized as 7,4'-dimethoxyflavanone (LI) (major) and I-2',II-2'-dihydroxy-I-4, II-4,I-4',II-4'-tetramethoxy-[I-β,II-3']-dihydrobichalcone (XLVI) (minor) by i.r., u.v., mass and n.m.r. spectroscopy. A gummy dark brown mixture of polymeric products was eluted with ethyl acetate.


CH3O
OH
OCH3
O
(XLV)
Cu(OAc)2-HClO4-HOAc
CH3O
OH
OCH3
O
CH3O
OH
OCH3
O
(XLVI)
+
CH3O
O
OCH3
O
(LI)
+
Polymeric mixture

Characterization of 7,4'-dimethoxyflavanone (LI)

The product melting at 93-4°C gave negative alc. $FeCl_3$ test and pink colour with Mg-HCl. The nature of the ring C was easily established with the help of its infra-red spectrum which displayed absorption band at 1675 cm^{-1}. The ultra-violet spectrum of this compound confirmed it to be a flavanone. U.v. spectrum exhibited two bands at 270 and 310 nm. The structure was easily elucidated with the help of n.m.r. spectrum.

N.m.r. spectrum of the product displayed the methoxyl protons as a singlet at δ 3.80 integrating for six protons. A multiplet at δ 2.86 for two protons was unmistakably assigned to the C-3 protons. The proton on the C-2 was seen as a doublet of doublet at δ 5.36 (J_{trans}=11 Hz, J_{cis}=5 Hz). Protons on the p-substituted ring B were observed as a pair of doublets at δ 6.90 and 7.40 (J=9 Hz) each for two protons and showing the A_2B_2 pattern. These signals were ascribed to C-3',5' and C-2',6' protons, respectively. One more doublet in the aromatic region at δ 7.84 (J=9 Hz) for one proton was due to the proton on the C-5 of the ring A. A highfield doublet (J=2.5 Hz) at δ 6.46 for one proton was imputed to the C-8 proton. A doublet of doublet at δ 6.56 (J_1=2.5 Hz, J_2=9 Hz) for one proton could only be assigned to the C-6 proton. The chemical shifts of protons of compound, LI, are given in table VI. The compound was, thus, identified as 7,4'-dimethoxyflavanone (LI).

Table-VI: Chemical shifts of protons of 7,4'-dimethoxyflavanone (LI).

Proton assignment	Chemical shifts (∂ ppm)
H-3	2.86 (mc, 2H)
MeO-7,4'	3.80 (s, 6H)
H-2	5.36 (dd, J_{trans}=11 Hz, J_{cis}=5 Hz, 1H)
H-8	6.46 (d, J=2.5 Hz, 1H)
H-6	6.56 (dd, J_1=2.5 Hz, J_2=9 Hz, 1H)
H-3',5'	6.90 (d, J=9 Hz, 2H)
H-2',6'	7.40 (d, J=9 Hz, 2H)
H-5	7.84 (d, J=9 Hz, 1H)

s= singlet, d= doublet, dd= doublet of doublet, mc= multiplet centred at; Spectrum run in $CDCl_3$ at60 MHz and TMS as internal standard ∂ 0.00.

The structure of the compound was further substantiated by the mass spectrometry (Chart VII). Its mass spectrum displayed peaks at m/z 150 and 134 corresponding to usual RDA fragments. The peak at m/z 134 was the base peak. The loss of ring B as the radical from the molecular ion gave an ion at m/z 177. The peak at m/z 161 was due to the p-methoxycinnamoyl cation and was indicative of the flavanone-chalcone isomerization. The peaks at m/z 121 and 135 were corresponding to the other usual ring B fragments. A peak at m/z 119 may be due to ion derived from the ion at m/z 134 by the loss of methyl group.

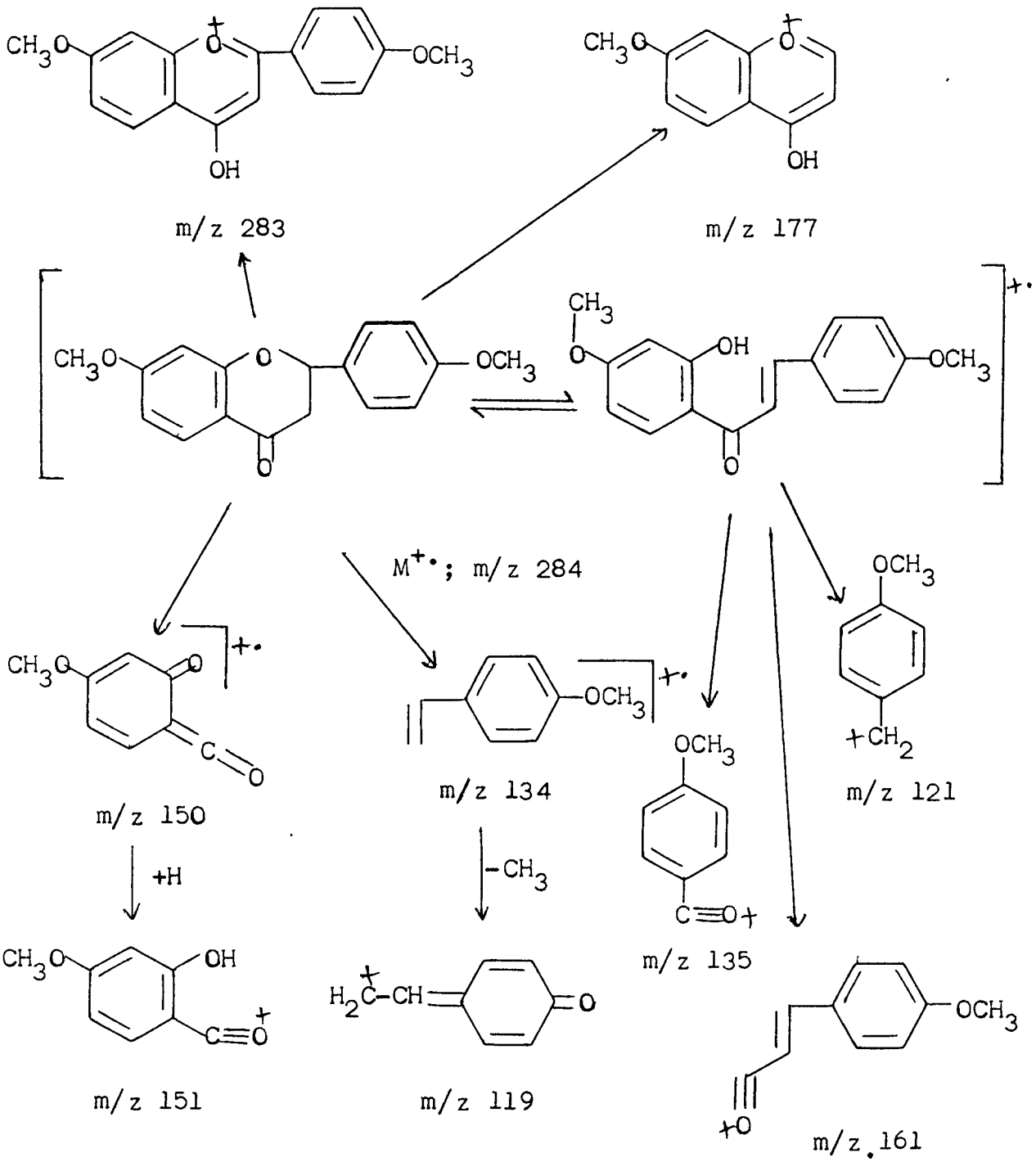
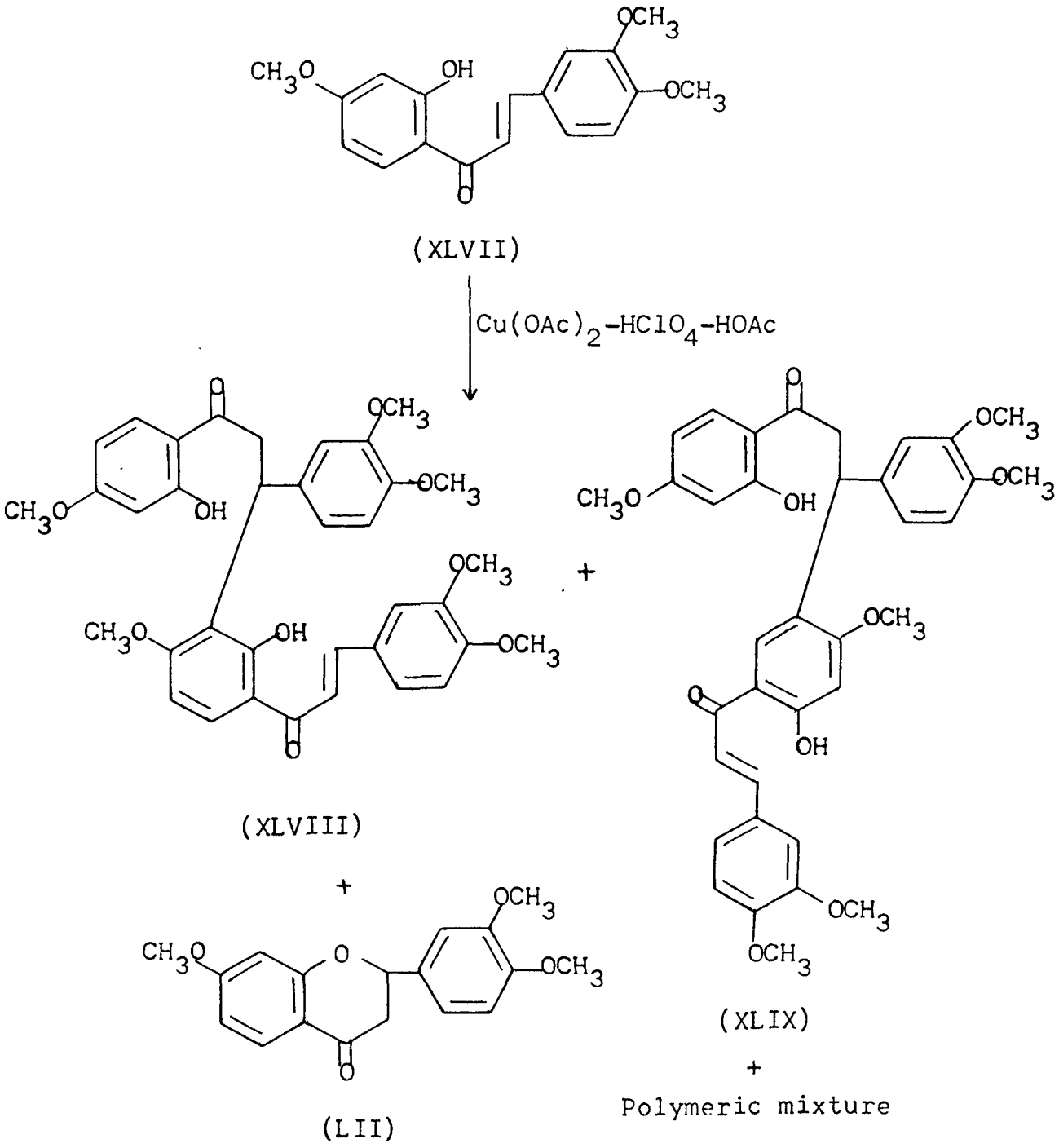

m/z 283
m/z 177
M+•; m/z 284
m/z 150
+H
m/z 151
m/z 134
-CH3
m/z 119
m/z 135
m/z 121
m/z 161

Chart VII

Reaction of 2'-hydroxy-3,4,4'-trimethoxychalcone (XLVII) with copper(II) acetate in the presence of perchloric acid

The reaction was carried out in a similar fashion. To a solution of copper(II) acetate in acetic acid were added perchloric acid and 2'-hydroxy-3,4,4'-trimethoxychalcone (XLVII). The reaction mixture was heated on a water bath for eight hours after keeping at room temperature for ten days which revealed no change. The reaction on usual work up and column chromatography yielded three products. The major product isolated in this reaction was identified as 7,3',4'-trimethoxyflavanone (LII) by spectral methods. Two more products obtained were found identical in all respects (m.m.p., i.r., u.v., n.m.r. and mass) to authentic samples of I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII) and I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-5']-dihydrobichalcone (XLIX). A complex mixture of polymeric products was obtained when the column was finally eluted with ethyl acetate.


(XLVII)
Cu(OAc)2-HClO4-HOAc
(XLVIII)
+
(XLIX)
+
Polymeric mixture
+
(LII)

Characterization of 7,3',4'-trimethoxyflavanone (LII)

This compound, m.p.117-8°C, showed in its mass spectrum the molecular ion, $M^{+\bullet}$ at m/z 314. The compound gave light pink colour with Mg-HCl indicating it to be a flavanone. The compound gave negative alcoholic $FeCl_3$ test showing the absence of hydroxy group which was further confirmed by its i.r. spectrum. The carbonyl band, observed at 1670 cm^{-1}, confirmed the nature of the compound as flavanone, Its u.v. spectrum exhibited absorption maxima at 234, 274 and 310 nm. The structure of this compound was easily elucidated as 7,3',4'-trimethoxyflavanone (LII) by its n.m.r. and mass spectra.

N.m.r. spectrum exhibited a multiplet at ð 2.94 for two protons which was ascribed to C-3 methylene protons. The signal for the C-2 proton was observed as a doublet of doublet (J_{trans}=11 Hz, J_{cis}=5 Hz) at ð 5.45. Two singlets at ð 3.86 and 3.95 integrating for three and six protons, respectively, were assigned to the protons of three methoxy groups. Aromatic region of the spectrum displayed a multiplet centred at ð 7.04 for three ring B protons. A downfield doublet (J=9 Hz) at ð 7.90 for one proton was attributed to the C-5 proton. A meta-coupled doublet at ð 6.55 (J=3 Hz) for one proton was due to the C-8 proton. The signal for C-6 proton was observed as a doublet of doublet (J_1=9 Hz, J_2=3 Hz) at ð 6.64. The chemical shifts of protons of the compound, LII, are given in table VII.

Table-VII: Chemical shifts of protons of 7,3',4'-trimethoxy-flavanone (LII).

Proton assignment	Chemical shifts
H-3	2.94 (mc, 2H)
MeO-3'	3.86 (s, 3H)
MeO-7,4'	3.95 (s, 6H)
H-2	5.45 (dd, J_{trans}=11 Hz, J_{cis}=5 Hz, 1H)
H-8	6.55 (d, J=3 Hz, 1H)
H-6	6.64 (dd, J_1=9 Hz, J_2=3 Hz, 1H)
H-2',5',6'	7.04 (mc, 3H)
H-5	7.90 (d, J=9 Hz, 1H)

s= singlet, d= doublet, dd= doublet of doublet, mc= multiplet centred at; Spectrum run in $CDCl_3$ at 60 MHz and TMS as internal standard δ= 0.00.

The structure was further supported by its mass spectrum (Chart VIII). The molecular ion peak at m/z 314 was only 10.97%. Diagnostic fragments in the spectrum were at m/z 150 and 164 (base peak), resulting from the RDA fragmentation of the molecular ion. A peak at m/z 151 can be attributed to either the ring A fragment or to the benzyl cation, a characteristic ring B fragment. The peak at m/z 177 is due to the fragment resulting by the loss of ring B from the molecular ion. Other usual fragments at m/z 313, 191, 165, 152, 149, 137, 135, 122 and 121 were also present.

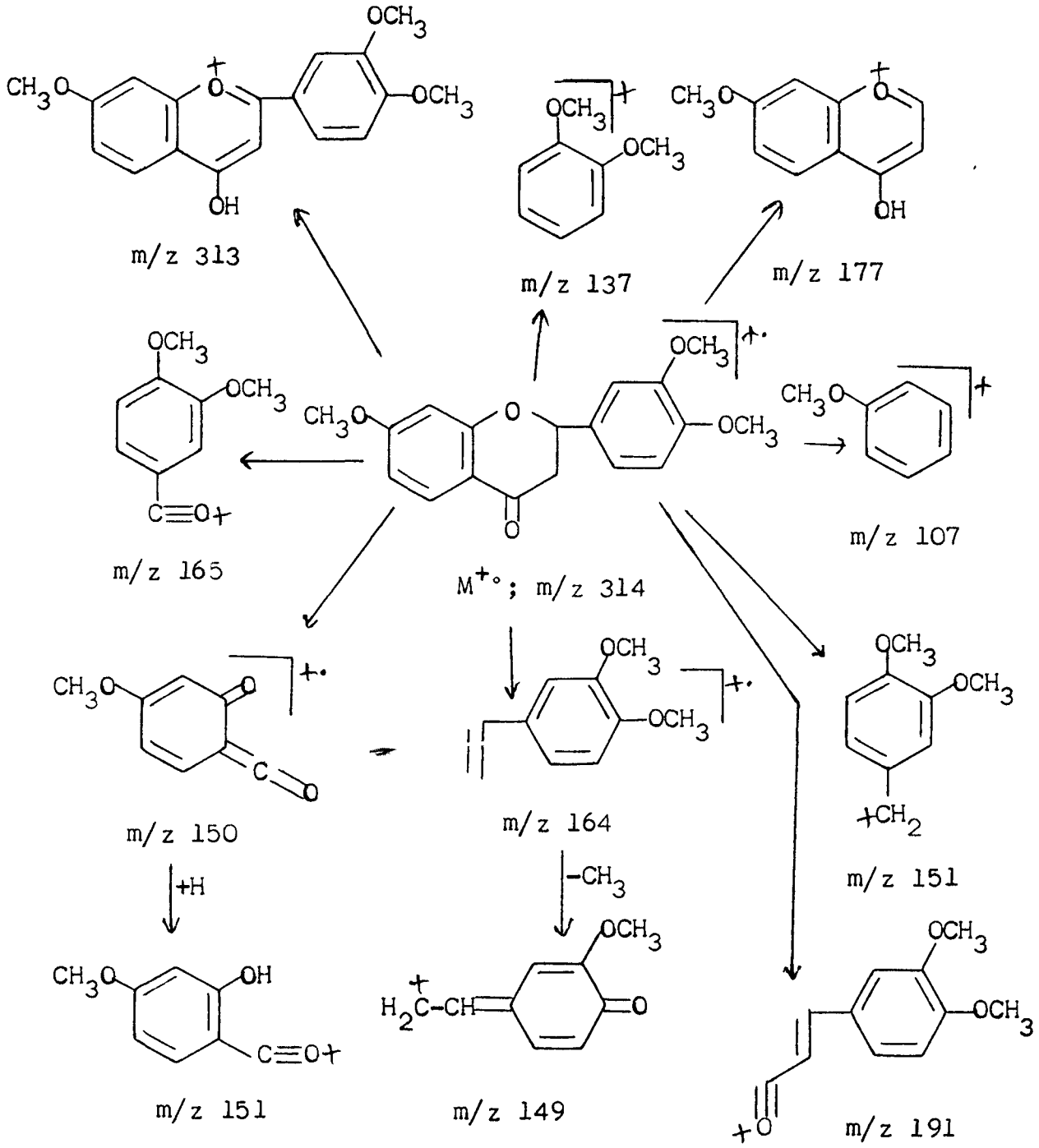

m/z 313
m/z 137
m/z 177
m/z 165
m/z 107
M+°; m/z 314
m/z 150
m/z 164
m/z 151
+H
-CH3
m/z 151
m/z 149
m/z 191

Chart VIII

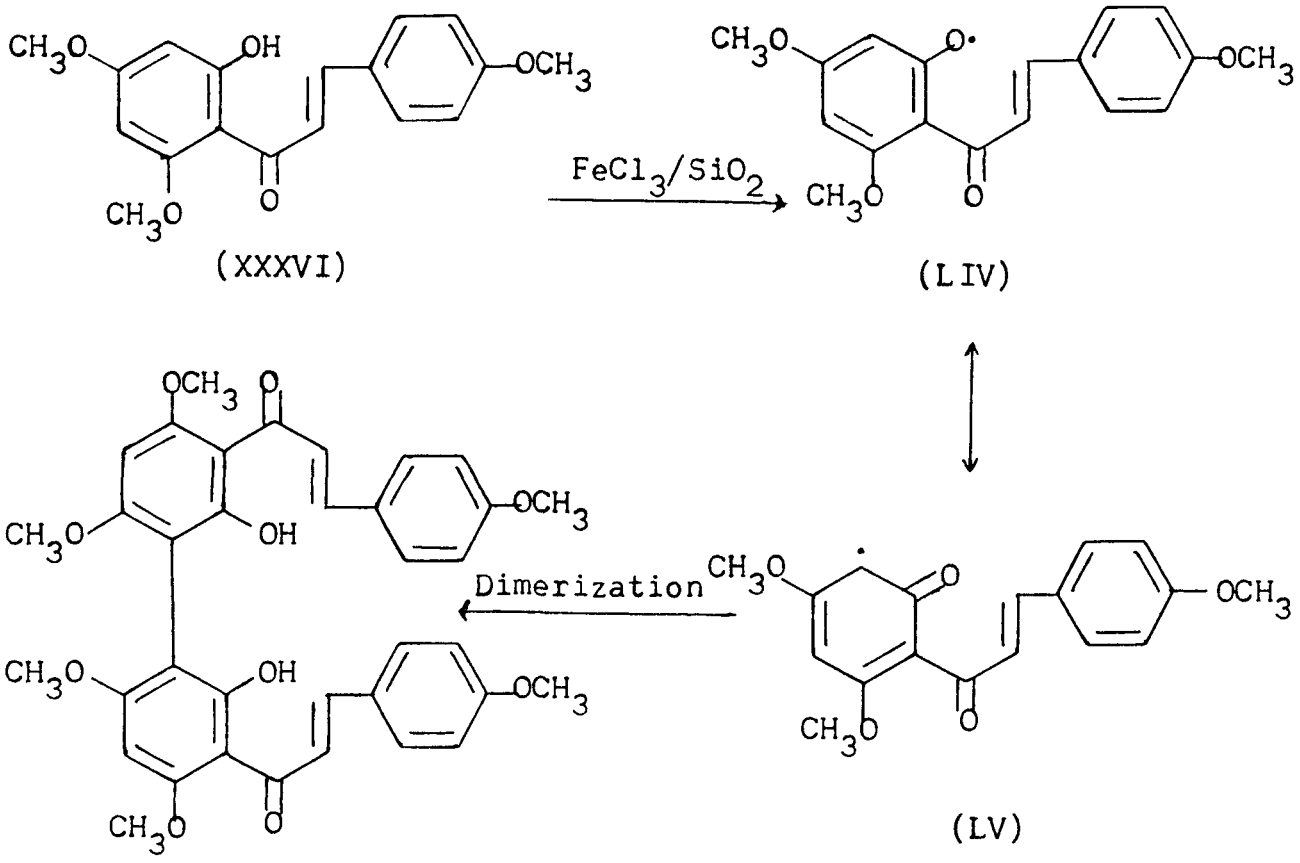
The results of the oxidation studies on the 2'-hydroxychalcones can be summarized as follows. The reaction of chalcones with silica bound ferric chloride produced major amount of polymeric products and the compounds which could only be isolated, in all the cases, were dihydrobichalcones. The reaction of chalcones with copper(II) acetate in the presence of perchloric acid in acetic acid gave flavanones as the major products alongwith minor amounts of dihydrobichalcones. In the case of 2,3-dimethylphenol, $[Fe(DMF)_3Cl_2][FeCl_4]$ complex in heterogeneous medium, although, proved a better coupling reagent, the reaction of $[Fe(DMF)_3Cl_2]$ $[FeCl_4]$ with 2'-hydroxychalcones in heterogeneous medium at room temperature revealed almost no change even after 24 hours.

The noteworthy point of these studies is the lack of oxidation on ring A, although in every case a free phenolic group (hydrogen-bonded) was present at C-2' position. An exception being the reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI) with silica bound ferric chloride in which [I-3',II-3']-bichalcone (XXXVIII) was obtained as a minor product. This is in line with the observations on natural systems by Brown[77] who states

'..... it has been found that certain hydroxylated anthraquinones and anthrones e.g. alizarin-2-glucoside, are not oxidized in the presence of laccase, probably as the result of strong hydrogen bonding between the 1-hydroxy group and the carbonyl

group that makes the molecules resistant to the formation of aryloxy radicals'.

The reaction of 2'-hydroxy-4,4'-dimethoxychalcone (XLV) with silica bound ferric chloride yielded I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4'-tetramethoxy-[I-β,II-3']-dihydrobichalcone (XLVI), while two dihydrobichalcones, I-2',II-2'-dihydroxy-I-3, II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII) and I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-5']-dihydrobichalcone (XLIX), were obtained in the reaction of 2'-hydroxy-3,4,4'-trimethoxychalcone (XLVII). The reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI) and silica bound ferric chloride gave I-2',II-2'-dihydroxy-I-4,II-4, I-4',II-4',I-6',II-6'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XXXVII) as the major product besides three minor products. Of the three, two minor products could not be fully characterized and what can be said regarding these compound is that they are probably the dihydrobichalcones. One minor product was partially characterized as I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4',I-6',II-6'-hexamethoxy-[I-3',II-3']-bichalcone (XXXVIII). The formation of [I-3',II-3']-bichalcone (XXXVIII) can be explained in terms of self coupling of mesomeric radical (LV) followed by enolization (Scheme II). The oxidation of the hydroxy group on the C-2' generates a radical on the oxygen atom which delocalizes to give mesomeric radical (LV).



Scheme II

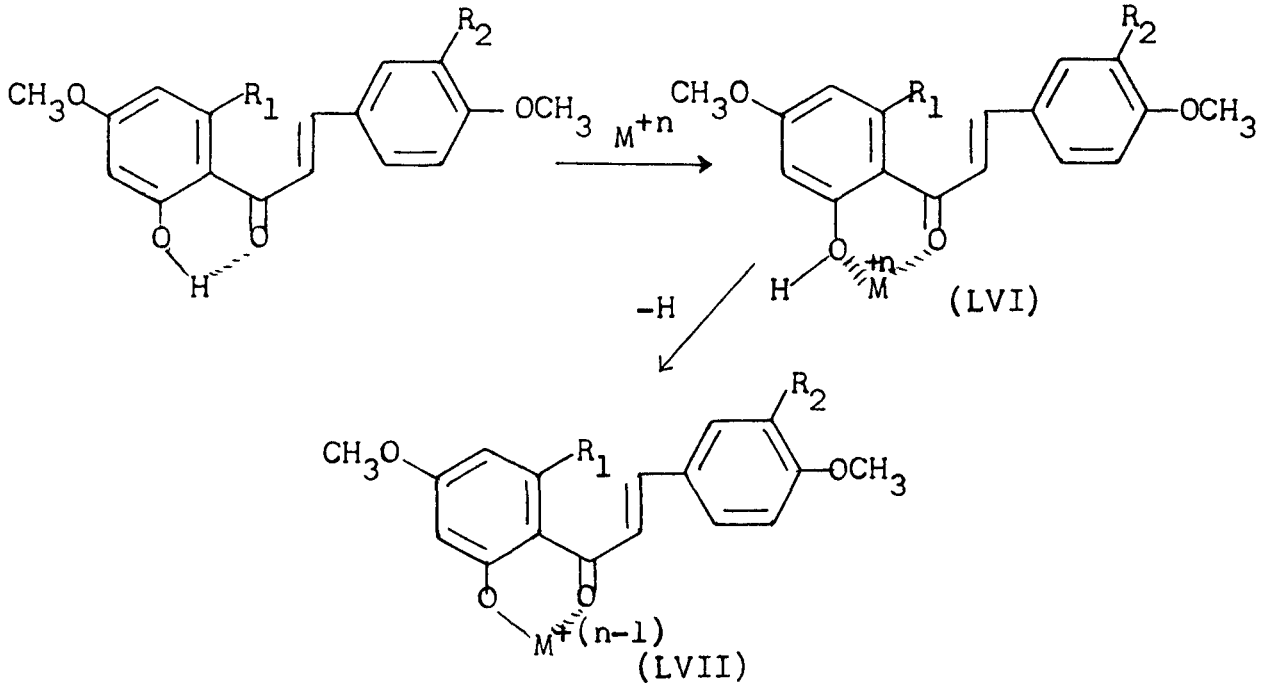
The reaction of 2'-hydroxy-4,4'-dimethoxychalcone (XLV) with copper(II) acetate-perchloric acid-acetic acid reagent system produced 7,4'-dimethoxyflavanone (LI) as the major product and I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4'-tetramethoxy-[I-β,II-3']-dihydrobichalcone (XLVI) as the minor product. 5,7,4'-Trimethoxyflavanone (L) was the main product in the reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI) with this reagent system besides one minor product identified as I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4',I-6',II-6'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XXXVII)..

The reaction of 2'-hydroxy-3,4,4'-trimethoxychalcone (XLVII) with this reagent system yielded 7,3',4'-trimethoxyflavanone (LII) as the main product besides two minor products which were characterized as I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII) and I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-5']-dihydrobichalcone (XLIX).

The cyclization of the 2'-hydroxychalcones to the corresponding flavanones may be explained in terms of catalysis either by metal ions or by acid. Acid-catalyzed chalcone-flavanone isomerization is well known[39]. However, in many metal ion catalytic reactions, the role of the metal ions is similar to that of a proton, but in a more efficient way because more than a single positive charge can be involved. Commonly, transition metals have 'd' orbitals which are only partially filled with electrons. In solution these positively charged metal-ions can readily combine with negative ions or other small electron donating chemical functions called ligands to form complex ions. The metal ion can form many bonds to the substrate and draw electron density from it, thus behaving as a superacid[78].

The formation of dihydrobichalcones in the reactions of 2'-hydroxychalcones with silica bound ferric chloride and copper(II) acetate-perchloric acid-acetic acid reagent system can be explained in terms of metal-ion catalysis. It can be assumed that the

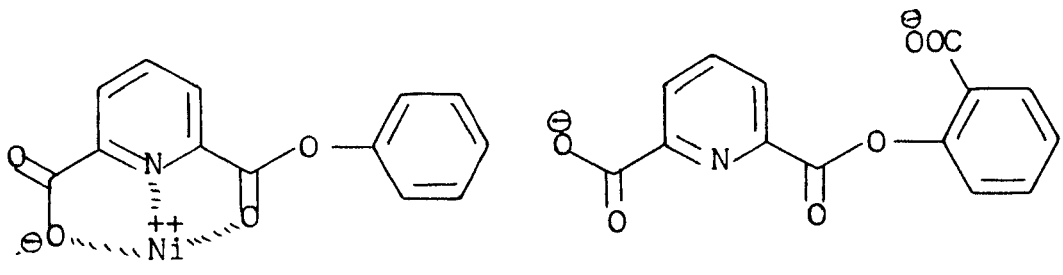
coordination takes place between the metal ion and hydroxy as well as carbonyl functions of the chalcones. Electron delocalization in the aromatic ring upon complexation with the metal ion increases, considerably, the acidity of the hydroxy group and the complex (LVI) loses a proton to form a six-membered metal chelate (LVII)[10]. Catalysis occurs, probably, as a result of the coordination of the metal ion with carbonyl group. The metal ion polarises the carbonyl function, thereby drawing electron density from the β-carbon and developing a partial positive charge.

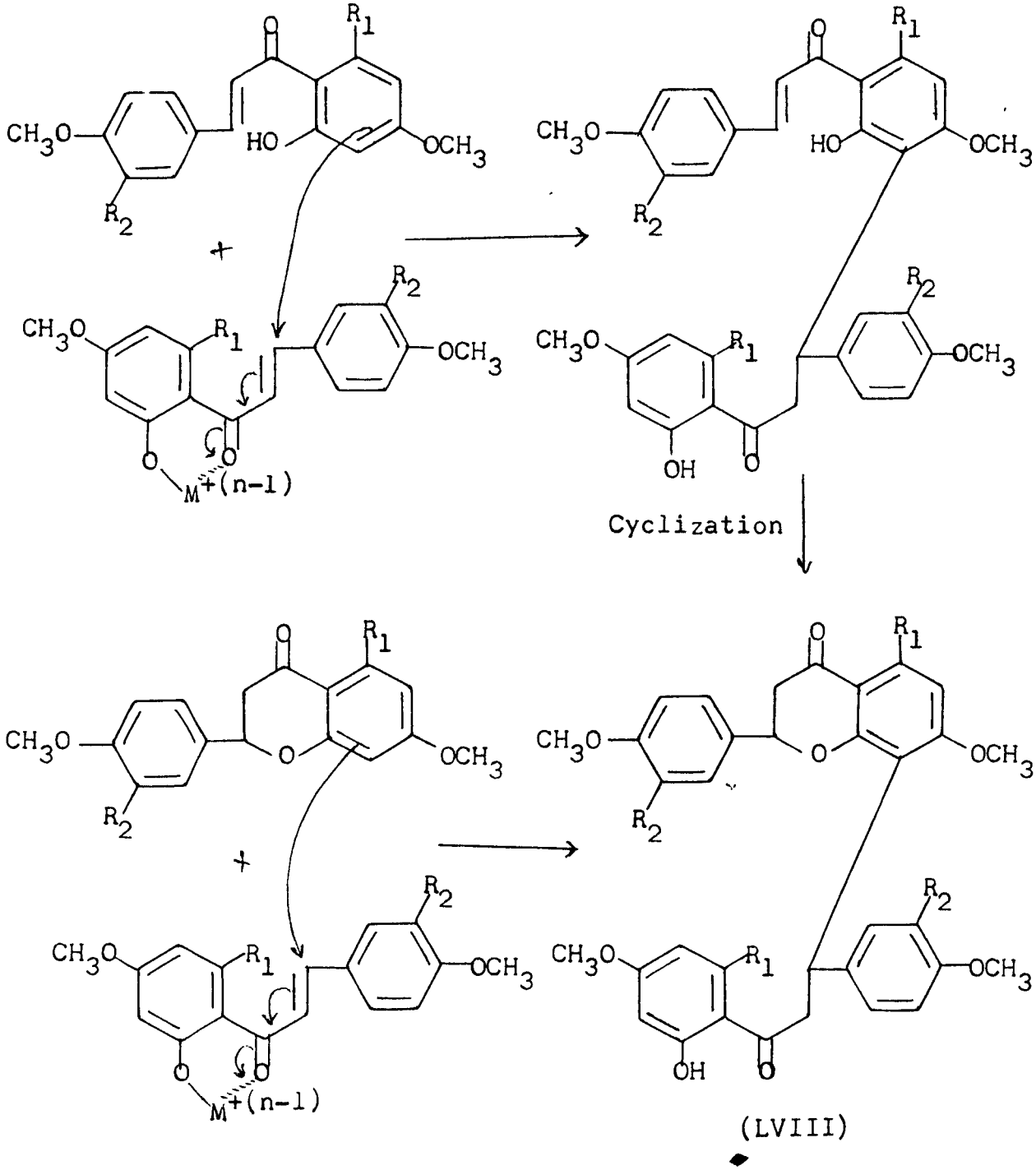


The attack by the aromatic ring of another chalcone molecule at the β carbon atom seems not feasible as there will be much inter-electronic repulsion. However, if it be assumed that

the electron-rich ring A of a chalcone molecule attacks at the β carbon atom to give dihydrobichalcone, there seems no reason to explain why the ring A of a flavanone molecule did not attack at the β carbon atom, in the reaction of chalcones with copper(II) acetate-perchloric acid-acetic acid system, forming flavanonyl-dihydrochalcone (LVIII) (Scheme III). Moreover, although the copper(II) acetate-perchloric acid-acetic acid reagent system proved an efficient catalyst for the chalcone-flavanone isomerization, the chalcone unit of the dihydrobichalcone did not cyclize, in any case, suggesting that the 2'-hydroxy group of the chalcone unit of dihydrobichalcone is probably not free. This points to a different reaction mechanism.

To understand the role of metal ion in these reactions, let us examine few models. The rate of hydrolysis of the ester function of the phenyl and salicyl esters of pyridine-2,6-dicarboxylic acid is significantly enhanced upon complexation with Ni(II) or Zn(II) ions[79].

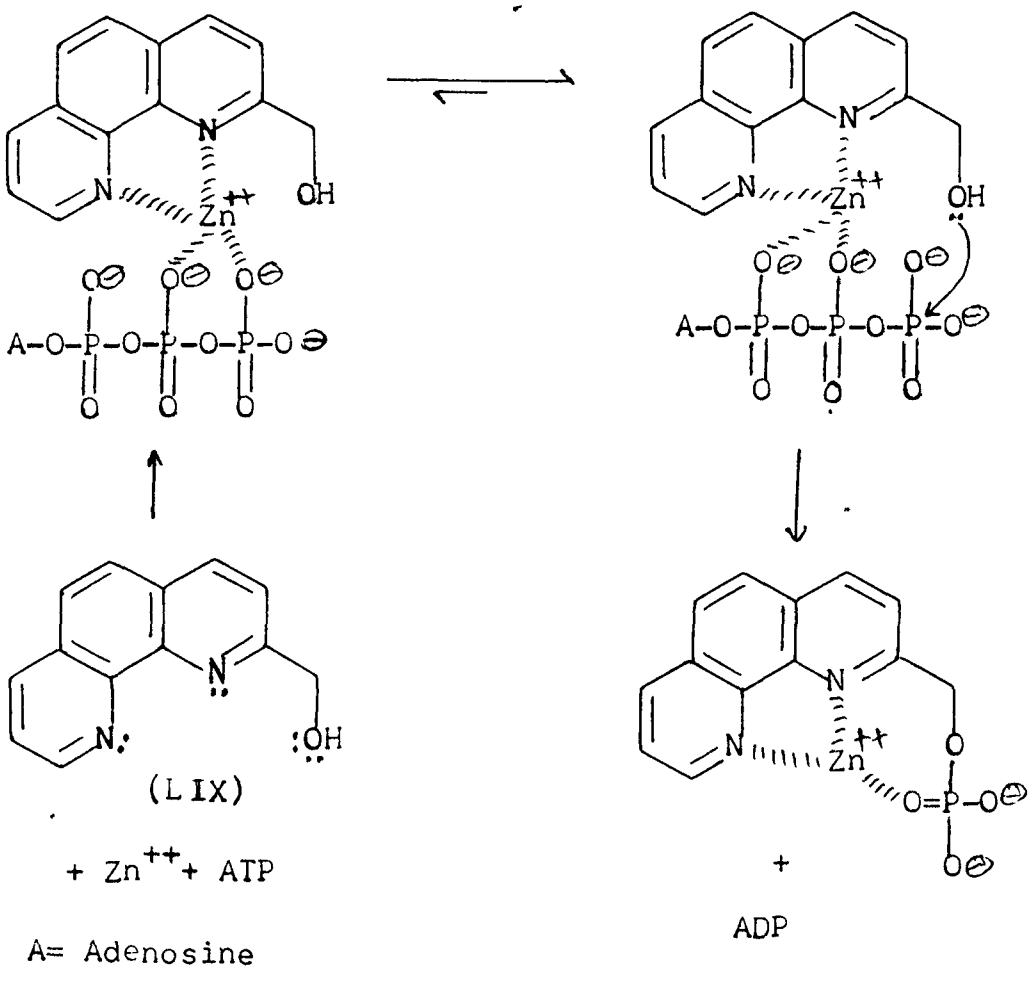




Scheme III

The relative rate with Ni(II) is 9300-fold with the phenyl ester and 3100-fold with the salicyl ester. In the latter case the rate is slower presumably because two anionic sites are in competition for the metal cation. But the reaction rate is almost twice as fast if the second carboxylic group is ionized, suggesting that carboxylate exerts a weak catalytic effect.

Similarly, phosphorylation of 2-hydroxymethylphenanthroline (LIX) by ATP is facilitated by Zn(II) complexation[80] (Scheme IV).

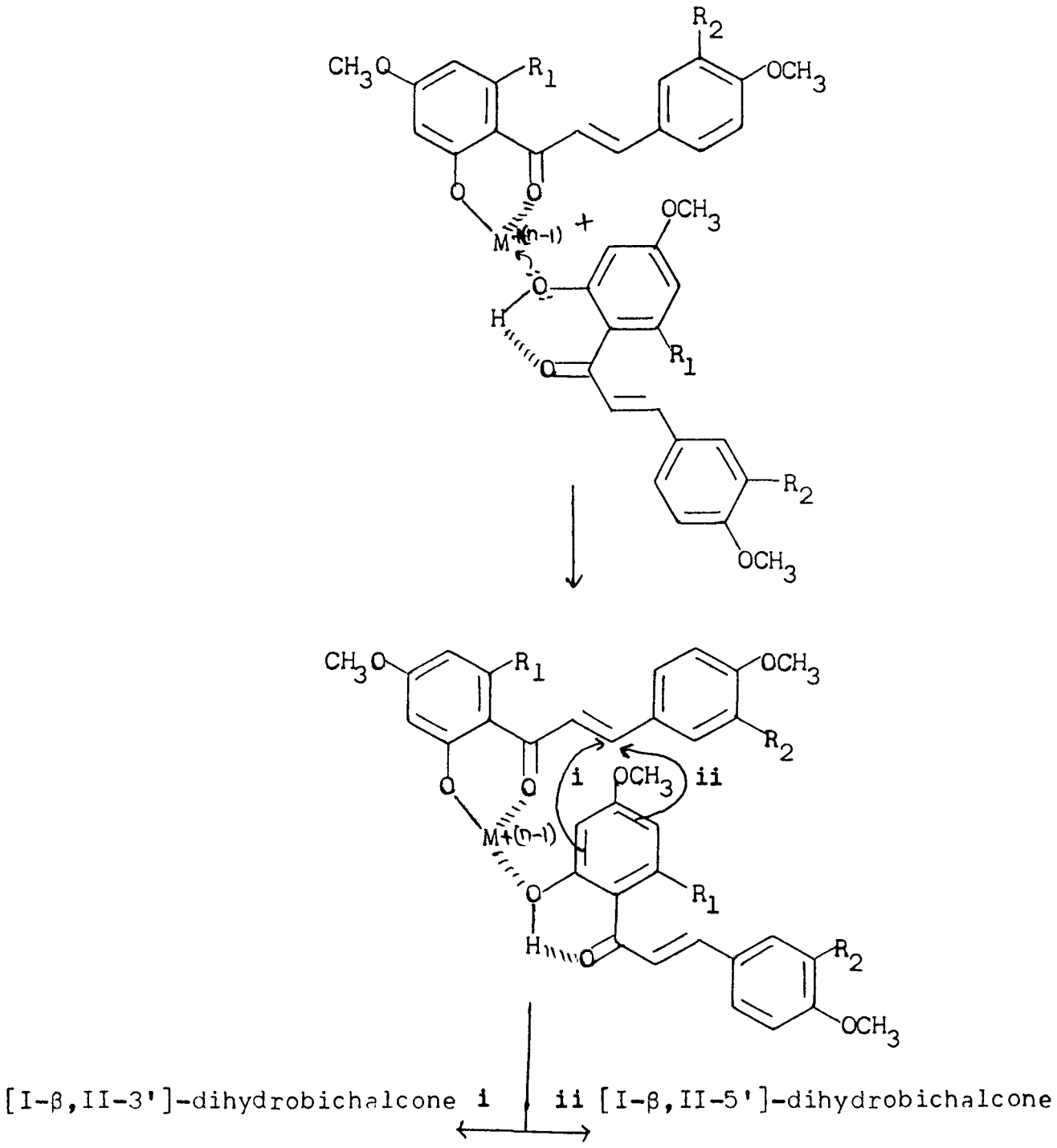


Scheme IV

This example illustrates the catalytic influence of a chelated metal ion. The metal ion has a directional effect or template effect as is seen by the binding together of ATP and phenanthroline. In addition it serves a neutralization function, thus reducing the electronic repulsion between the incoming hydroxy methyl group and the phosphate of ATP.

These examples provide, to some extent, an idea about the role of metal ions in the reactions of 2'-hydroxychalcones. A plausible mechanism, in the light of availabe literature, for the formation of [I-β,II-3']- and [I-β,II-5']-dihydrobichalcones can be written as in scheme V.

It is evident from the mechanism outlined in scheme V that the metal ion in the metal chelate (LVII) further co-ordinates with the hydroxy group of the other chalcone molecule, thereby reducing the inter-electronic repulsion and bringing the electron-rich ring A closer to the β carbon atom. The nucleophilic attack by the ring A can now take place at the electron-deficient β carbon atom. The ring A can attack either through C-3' or C-5' to give [I-β,II-3']-dihydrobichalcones or [I-β,II-5']-dihydrobichalcones. While the reaction of chalcones (XXXVI, XLV) produced, in both the cases, only [I-β,II-3']-dihydrobichalcones (XXXVII, XLVI), the [I-β,II-5']-dihydrobichalcone (XLIX) was obtained in major amount compared to [I-β,II-3']-dihydrobichalcone (XLVIII) in the case of 2'-hydroxy-3,4,4'-trimethoxychalcone (XLVII). This can be attributed to some steric factors.



Scheme 5

Our results are interesting both from the biogenetic as well as synthetic point of views. The formation of I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4',I-6',II-6'-hexamethoxy-[I-3',II-3']-bichalcone (XXXVIII) by the phenol oxidative coupling provides first experimental evidence to the fact that the coupling takes place at the chalcone stage in the biosynthesis of biflavonoids. Metal-catalyzed intermolecular addition of an aromatic ring to an α,β-unsaturated system seems novel and of potential synthetic importance in the synthetic organic chemistry. Such type of reactions are not generally found in the literature, though acid-catalyzed intramolecular 1,4-addition of ring A of chalcone to α,β-unsaturated system is reported[81]. The role of the metal ions in these reactions is similar to their role in biological systems. They have a template or directional effect and served a neutralization function in bringing the reacting sites closer. 2'-Hydroxychalcones are believed to be the intermediates in the biosynthesis of flavonoids and biflavonoids and are frequently encountered in nature. In the event of presence of 2'-hydroxychalcones together with the metal ions in the biological system, the possibility of formation of dihydrobichalcone in plants can not be ruled out, though no report on their isolation from a natural source has yet appeared.

EXPERIMENTAL

All the melting points were recorded on Kofler microscopical hot stage and are uncorrected. Infra-red spectra were obtained on a Pye Unicam SP3-100 spectrophotometer. Ultra-violet spectra were measured on a Pye Unicam PU8800 instrument. Nuclear magnetic resonance spectra were recorded on 60 MHz Varian A60D, 80 MHz Varian CFT-20 or 100 MHz FX-100 instruments using tetramethylsilane (TMS) as internal standard. All the chemical shift values are given in ppm down field from TMS (δ= 0). The abbreviations, s, d, mc, t and dd denote singlet, doublet, multiplet centred at, triplet and doublet of doublet, respectively. Mass spectra were recorded with a JEOL JMS-D300 spectrometer at 70 eV. All the reagents used were of BDH grade and purification of the commercial solvents was done before use. Silica bound ferric chloride was prepared by following the Jempty and Miller procedure[82], while $[Fe(DMF)_3Cl_2][FeCl_4]$ complex was prepared according to Tobinaga et al. method[83]. Starting chalcones were prepared by the alkali condensation of suitably substituted acetophenone and benzaldehyde by either cold or hot condensation[84].

Preparation of 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI)

To a mixture of phloroacetophenone-4,6-dimethylether (5.00 g, 25.5 mmol) and p-anisaldehyde (3.47 g, 25.5 mmol) in alcohol (50 ml) was added hot 50% aqueous solution of sodium hydroxide (10 g). The reaction mixture was heated at 50°C for

30 minutes. The contents were then cooled, poured into cold water and neutralized with dilute hydrochloric acid. A yellow solid was obtained which was filtered, washed with water, dried and crystallized from alcohol to yield yellow needles of 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI) (5.85 g), m.p.112-3°C.

Preparation of 2'-hydroxy-4,4'-dimethoxychalcone (XLV)

To a cold suspension of equimolar amounts of 2-hydroxy-4-methoxyacetophenone (8.00 g, 50 mmol) and p-anisaldehyde (7.00 g, 50 mmol) in alcohol (16 ml) was added a cold 60% aqueous solution of potassium hydroxide (95.00 g). The flask was stoppered securely and allowed to stand at room temperature for one week with occasional shaking. The contents were then poured into ice, neutralized with dil. HCl to get a yellow precipitate. The solid was filtered, washed with water, dried and crystallized from methanol to afford yellow needles of 2'-hydroxy-4,4'-dimethoxychalcone (XLV) (10.4 g), m.p.89-91°C.

Preparation of 2'-hydroxy-3,4,4'-trimethoxychalcone (XLVII)

To the cold solution of 2-hydroxy-4-methoxyacetophenone (8.00 g, 50 mmol) and 3,4-dimethoxybenzaldehyde (8.00 g, 50 mmol) in alcohol (20 ml) was added with shaking a 60% aqueous solution of potassium hydroxide (95.00 g). The contents were then stoppered and left at room temperature for one week with occasional shaking.

The reaction mixture was then poured into cold water, neutralized with dilute hydrochloric acid. A yellow solid precipitated which was filtered, washed with water, dried and crystallized from alcohol to yield yellow needles of 2'-hydroxy-3,4,4'-trimethoxy-chalcone (XLVII) (10.75 g), m.p.150-2°C.

Reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI) with silica bound ferric chloride

2'-Hydroxy-4,4',6'-trimethoxychalcone (10.00 g, 32 mmol), dissolved in dichloromethane (150 ml), was poured into a round bottomed flask containing ferric chloride (10.40 g, 64 mmol) adsorbed on appropriate amount of silica gel. A colour change from yellow to green and finally to the dark brown was observed. The solvent was then evaporated on a rotary evaporator under reduced pressure and the reaction mixture was left rotating at room temperature. The progress of the reaction was monitored by t.l.c. at an interval of one hour. The reaction was terminated after six hours by adding water (125 ml) and dichloromethane (200 ml). After the removal of the aqueous layer, the dichloromethane layer was washed several times with water till the water layer was colourless and neutral to litmus. The contents were then dried over anhydrous sodium sulphate and solvent evaporated to give a gummy mass (8.20 g). The gummy mass, which revealed five spots besides base products on silica gel t.l.c. plate using benzene:acetone (23:2) as the

developer, was adsorbed on silica gel (60-120 mesh) and subjected to column chromatography. Elution of the column with petrol: benzene (1:1) afforded unreacted 2'-hydroxy-4,4',6'-trimethoxy-chalcone (1.75 g). Further elution with benzene:ethyl acetate (49:1) yielded an orange solid which was crystallized from chloroform-methanol mixture as dark orange crystal (326 mg), m.p.222-4°C, and characterized as I-2',II-2'-dihydroxy-I-4,II-4, I-4',II-4',I-6',II-6'-[I-β,II-3']-dihydrobichalcone (XXXVII). A yellow solid was obtained when the column was eluted with benzene: ethyl acetate (18:1) which was crystallized from pyridine-methanol mixture as yellow crystals of I-2',II-2'-dihydroxy-I-4,II-4,I-4', II-4',I-6',II-6'-hexamethoxy-[I-3',II-3']-bichalcone (XXXVIII) (35 mg), m.p.288-90°C (lit.[65] m.p.289-91°C). Elution of the column with benzene:ethyl acetate (97:3) furnished a dark brown solid, crystallized from benzene-acetone as brown crystals of compound (XXXIX) (13 mg), m.p.158-60°C. Further elution of the column with benzene:ethyl acetate (47:3) afforded another solid which was crystallized from benzene as yellow crystals of compound (XL) (14 mg), m.p.183-6°C. Finally, the column was eluted with ethyl acetate, ethyl acetate-methanol mixture and methanol to give a complex mixture of polymeric products (3.5 g), m.p.>250°C.

I-2',II-2'-Dihydroxy-I-4,II-4,I-4',II-4',I-6',II-6'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XXXVII)

M.p. : 222-4°C

IR(KBr) : ν_{max} 3450, 3000, 2940, 1620, 1585, 1560, 1510, 1460, 1420, 1330, 1310, 1290, 1260, 1220, 1170, 1160, 1135, 1115, 1080, 1030, 980, 830 cm^{-1}.

UV(EtOH) : λ_{max} 290 and 365 nm.

NMR($CDCl_3$) : δ 3.68 (s, 3H, I-4-OMe), 3.80 (s, 3H, II-4-OMe), 3.81 (s, 3H, I-6'-OMe), 3.85 (s, 6H, I-4',II-6'-OMe), 3.92 (s, 3H, II-4'-OMe), 4.00 (d, J=8 Hz, 2H, I-α-H), 5.28 (t, J=8 Hz, 1H, I-β-H), 5.90 (d, J=3 Hz, 1H, I-3'-H), 5.99 (s, 1H, II-5'-H), 6.02 (d, J=3 Hz, 1H, I-5'-H), 6.79 (d, J=9 Hz, 2H, I-3,5-H), 6.92 (d, J=9 Hz, 2H, II-3,5-H), 7.35 (d, J=9 Hz, 2H, I-2,6-H), 7.55 (d, J=9 Hz, 2H, II-2,6-H), 7.76 (s, 2H, II-α,β-H), 13.86 (s, 1H, I-2'-OH), 14.25 (s, 1H, II-2'-OH).

MS(rel. int.) : m/z 629 (7.64), 628 (18.44), 613 (7.14), 510 12.85), 506 (6.24), 494 (14.84), 474 (15.21), 447 (32.66), 446 (26.84), 434 (9.08), 433 (30.32), 432 (7.64), 431 (9.53), 356 (8.12), 340 (6.05), 328 (18.67), 327 (28.41), 315 (91.28), 314

(42.86), 313 (100), 299 (13.25), 298 (63.72), 181 (84.38), 180 (12.15), 161 (11.95), 154 (32.64), 134 (16.39), 133 (10.20), 125 (23.87), and 121 (84.57).

I-2',II-2'-Dihydroxy-I-4,II-4,I-4',II-4',I-6',II-6'-hexamethoxy-[I-3',II-3']-bichalcone (XXXVIII)

M.p. : 288-90°C

IR(KBr) : ν_{max} 3450, 2920, 2850, 1620, 1601, 1560, 1510, 1470, 1445, 1330, 1260, 1220, 1175, 1125, 1040, 825 and 720 cm^{-1}.

UV($CHCl_3$) : λ_{max} 228 and 350 nm.

MS(rel. int.) : m/z 626 (100), 611 (6.62), 598 (7.53), 595 (9.58), 519 (5.79), 493 (8.63), 492 (15.47), 491 (9.92), 465 (10.92), 464 (25.43), 463 (63.80), 461 (31.51), 435 (20.38), 434 (17.56), 358 (10.29), 357 (7.55), 327 (30.43), 315 (15.79), 313 (5.49), 301 (25.87), 193 (12.59), 179 (8.74), 161 (35.85), 134 (30.68), 133 (17.53), 121 (35.96) and 119 (10.77).

Compound (XXXIX)

M.p. : 158-60°C

IR(KBr) : ν_{max} 3440, 2920, 1620, 1580, 1550, 1510, 1465, 1420, 1320, 1290, 1220, 1165, 1120, 1070, 1025, 980, 880, 830, 790, 725, 665 and 620 cm^{-1}.

UV($CHCl_3$) : λ_{max} 275 and 350 nm.

MS(rel. int.) : m/z 405 (5.41), 404 (22.54), 371 (5.56), 357 (3.57), 355 (2.97), 341 (3.51), 328 (2.38), 315 (5.27), 314 (9.66), 313 (14.64), 312 (2.97), 298 (2.97), 224 (4.17), 223 (8.34), 210 (13.03), 209 (100), 195 (14.28), 192 (33.31), 191 (7.14), 181 (49.99), 161 (4.72), 134 (14.28) and 121 (16.66).

Compound (XL)

M.p. : 183-6°C

IR(KBr) : ν_{max} 3400, 2910, 1620, 1510, 1465, 1415, 1290, 1250, 1215, 1170, 1120, 1030, 830, 795 and 720 cm^{-1}.

UV($CHCl_3$) : λ_{max} 275 and 350 nm

MS(rel. int.) : m/z 449 (1.15), 447 (1.47), 445 (1.39), 443 (1.64), 439 (1.69), 430 (1.02), 429 (2.33), 342 (1.12), 327 (1.00), 314 (11.22), 313 (52.15), 312 (39.87), 253 (9.28), 215 (21.79), 181 (35.45), 180 (18.34), 179 (20.47), 161 (19.38), 152 (15.45), 142 (100), 134 (58.27), 133 (13.24), 125 (40.00) and 121 (61.14).

Reaction of 2'-hydroxy-4,4'-dimethoxychalcone (XLV) with silica bound ferric chloride

2'-Hydroxy-4,4'-dimethoxychalcone (3.00 g, 10.5 mmol) was dissolved in dichloromethane (40 ml). This was then added to the ferric chloride (3.46 g, 21.0 mmol) bound to silica gel (34.00 g). An immediate colour change was observed. The solvent was removed on a rotary evaporator under reduced pressure and reaction mixture was left rotating for eight hours at room temperature. Water (50 ml) and dichloromethane (200 ml) were then added, the mixture was stirred, filtered and more dichloromethane was added. The organic phase was washed with water, dried (Na_2SO_4), and evaporated to give a brown gummy solid (2.75 g), which was subjected to column chromatography. Elution of the column with petrol-benzene (4:1) afforded 2'-hydroxy-4,4'-dimethoxychalcone (XLV) (0.495 g), m.p. 90°C. A bright yellow compound was eluted with petrol-benzene (1:1), crystallized from ether-ethyl acetate mixture as yellow crystals (20 mg), m.p. 173-4°C, and characterized as I-2',II-2'-dihydroxy-

I-4,II-4,I-4',II-4'-tetramethoxy-[I-β,II-3']-dihydrobichalcone (XLVI). Final elution of column with more polar solvents such as ethyl acetate and methanol gave a red gummy mass (1.850 g). T.l.c. examination of this mass revealed it to be a complex mixture of polymeric products.

I-2',II-2'-Dihydroxy-I-4,II-4,I-4',II-4'-tetramethoxy-[I-β,II-3']-dihydrobichalcone (XLVI)

M.p. : 173-4°C

IR(KBr) : ν_{max} 3430, 2920, 1630, 1600, 1555, 1510, 1465, 1450, 1420, 1370, 1280, 1240, 1210, 1165, 1120, 1040, 985, 820 and 620 cm^{-1}.

UV(EtOH) : λ_{max} 240, 275, 330 and 370 nm.

NMR($CDCl_3$) : δ 3.58 (mc, 2H, I-α-H), 3.79 (s, 3H, I-4-MeO), 3.81 (s, 6H, I-4',II-4-MeO), 3.86 (s, 3H, II-4'-OMe), 4.90 (t, J=8 Hz, 1H, I-β-H), 6.45 (mc, 3H, I-3',I-5',II-5'-H), 6.84 (d, J=9 Hz, 2H, I-3,5-H), 6.92 (d, J=9 Hz, 2H, II-3,5-H), 7.18 (d, J=15 Hz, 1H, II-α-H), 7.20 (d, J=9 Hz, 2H, I-2,6-H), 7.46 (d, J=9 Hz, 2H, II-2,6-H), 7.67 (d, J=15 Hz, 1H, II-β-H), 7.73 (d, J=9 Hz, 1H, I-6'-H), 7.78 (d, J=9 Hz, 1H, II-6'-H), 12.69 (s, 1H, I-2'-OH), 13.35 (s, 1H, II-2'-OH).

MS(rel. int.) : m/z 570 (5.39), 569 (14.02), 419 (6.77), 418 (19.56), 406 (7.39), 405 (26.96), 404 (100), 301 (12.56), 300 (5.24), 285 (14.27), 284 (23.87), 283 (2.49), 270 (67.58), 161 (12.53), 151 (37.55), 150 (5.26), 135 (15.24), 134 (20.96), 133 (17.56) and 121 (35.76).

Reaction of 2'-hydroxy-3,4,4'-trimethoxychalcone (XLVII) with silica bound ferric chloride

2'-Hydroxy-3,4,4'-trimethoxychalcone (5.00 g, 16 mmol), dissolved in dichloromethane (80 ml), was added to the ferric chloride (5.20 g, 32 mmol) adsorbed on silica gel (52.00 g). An immediate colour change from yellow to dark brown was observed. The solvent was then evaporated on a rotary evaporator under reduced pressure and the reaction mixture was left rotating at room temperature. The progress of the reaction was monitored by t.l.c. at an interval of two hours. The reaction was terminated after six hours by adding water (50 ml) and excess of dichloromethane. Aqueous layer was then removed and organic layer was washed several times with water, dried over anhydrous sodium sulphate and evaporated to yield a gummy solid (4.80 g). The t.l.c. of the crude solid in benzene:acetone (29:1) revealed it to be a mixture of three products besides polymeric products. The crude solid was then chromatographed over silica gel. Elution of the column with petrol-benzene

(1:1) afforded the unchanged starting material, 2'-hydroxy-3,4,4'-trimethoxychalcone (1.50 g). Further elution of the column with benzene yielded a yellow compound which was crystallized from ether-ethyl acetate mixture as bright yellow crystals (75 mg), m.p.155-6°C. This compound was characterized as I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII). Furthermore elution of column with benzene furnished another yellow compound which was crystallized from ethyl acetate as dark yellow crystals (90 mg), m.p.174-5°C, and characterized as I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-5']-dihydrobichalcone (XLIX). When column was finally eluted with ethyl acetate:acetone (1:1), a complex mixture of polymeric products was obtained as a tarry material (1.750 g).

I-2',II-2'-Dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII)

M.p. : 155-6°C

IR(KBr) : ν_{max} 3430, 2920, 1630, 1610, 1570, 1510, 1460, 1415, 1370, 1250, 1210, 1135, 1020, 990, 840, 750 and 650 cm^{-1}.

UV(EtOH) : λ_{max} 272, 314 and 375 nm.

NMR($CDCl_3$) : δ 3.57 (d, J=8 Hz, 2H, I-α-H), 3.82-3.93 (merged singlets, 18H, I-3,II-3,I-4,II-4,I-4',II-4'-OMe), 4.95 (t, J=8 Hz, 1H, I-β-H), 6.44 (mc, 3H, I-3',5', II-5'-H), 6.80 (s, 3H, I-2,5,6-H), 6.87 (d, J=9 Hz, 1H, II-5-H), 7.13 (mc, 2H, II-2,6-H), 7.37 (d, J=15 Hz, 1H, II-α-H), 7.73 (d, J=9 Hz, 2H, I-6',II-6'-H), 7.77 (d, J=15 Hz, 1H, II-β-H), 12.69 (s, 1H, I-2'-OH), 13.39 (s, 1H, II-2'-OH).

MS(rel. int.) : m/z 631 (2.12), 630 (8.25), 629 (20.23), 479 (4.05), 478 (12.56), 465 (27.51), 464 (100), 313 (7.59), 299 (57.55), 191 (12.58), 164 (10.83), 163 (7.54), 151 (5.91), 150 (50.77).

I-2',II-2'-Dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-5']-dihydrobichalcone (XLIX)

M.p. : 174-5°C

IR(KBr) : ν_{max} 3440, 2920, 1622, 1565, 1510, 1460, 1410, 1370, 1260, 1220, 1135, 1105, 1070, 1020, 975,and 790 cm^{-1}.

UV(EtOH) : λ_{max} 270, 320 and 375 nm.

NMR($CDCl_3$) : δ 3.81-3.94 (complex singlets, 20H, I-3,II-3,I-4, II-4,I-4',II-4'-OMe, I-α-H), 5.38 (t, J=8 Hz, 1H,

I-β-H), 6.43 (mc, 3H, I-3',5',II-3'-H), 6.77 (d, J=9 Hz, 1H, I-5-H), 6.90 (d,J=9 Hz,1H,II-5-H), 7.13 (mc, 4H, I-2,6,II-2,6-H), 7.39 (d, J=15 Hz, 1H, II-α-H), 7.81 (d, J=9 Hz, 1H, I-6'-H), 7.83 (d, J=15 Hz, 1H, II-β-H), 7.86 (s, 1H, II-6'-H), 12.77 (s, 1H, I-2'-OH), 13.83 (s, 1H, II-2'-OH).

MS(rel. int.) : m/z 630 (17.57), 629 (47.55), 478 (12.59), 466 (18.13), 465 (55.59), 464 (22.56), 437 (26.67), 315 (5.83), 314 (22.54), 313 (82.34), 299 (37.51), 287 (5.97), 191 (5.78), 178 (19.24), 164 (7.55), 151 (100) and 150 (10.89).

Reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (XXXVI) with copper(II) acetate in the presence of perchloric acid

2'-Hydroxy-4,4',6'-trimethoxychalcone (3.00 g,9.6 mmol) was added to a solution of copper(II) acetate (3.0 g, 19.2 mmol) in glacial acetic acid (125 ml) and 70% perchloric acid (9.8 ml, 115.2 mmol). The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by thin layer chromatography. The ratio of the base products started increasing slowly after fifteen days. The reaction mixture, after stirring for an additional five days, was poured into a dilute solution of sodium bicarbonate. A brown precipitate was obtained which was extracted with ethyl acetate. The ethyl acetate layer was washed

with water, dried over anhydrous sodium sulphate and evaporated to give a crude yellow solid (2.98 g). The t.l.c. examination of this solid revealed it to be a mixture of three compounds besides base products. The solid was subjected to column chromatography over silica gel. Elution of the column with petrol-benzene (1:1) afforded unreacted 2'-hydroxy-4,4',6'-trimethoxychalcone (0.955 g), m.p.113°C. A dark orange compound was eluted with benzene-ethyl acetate (99:1) which was crystallized from chloroform-methanol mixture as orange crystals (0.486 g), m.p.222-4°C. This product was found identical in all respects (m.m.p., i.r., u.v., n.m.r. and mass) to an authentic sample of I-2',II-2'-dihydroxy-I-4,II-4,I-4', II-4',I-6',II-6'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XXXVII). Further elution of the column with benzene-ethyl acetate (19:1) afforded a white product which was crystallized from chloroform: ethyl acetate mixture as white cubes (0.820 g), m.p.121-2°C. This compound was characterized as 5,7,4'-trimethoxyflavanone (L). Furthermore elution of the column with ethyl acetate yielded polymeric products (0.1 g).

5,7,4'-Trimethoxyflavanone (L)

M.p. : 121-2°C

IR(KBr) : ν_{max} 2945, 2920, 2815, 1660, 1610, 1575, 1510, 1480, 1450, 1420, 1380, 1360, 1330, 1310, 1300, 1250, 1210, 1170, 1150, 1100, 1080, 1035, 1000, 960, 940, 880, 860, 830, 810, 800, 740, 730, 705, 680 and 640 cm^{-1}.

UV(EtOH) : λ_{max} 283 and 320 nm.

NMR($CDCl_3$) : δ 2.84 (mc, 2H, 3-H), 3.80 (s, 9H, 5,7,4'-OMe), 5.25 (dd, J_{trans}=11 Hz, J_{cis}=5 Hz, 1H, 2-H), 6.00 (s, 2H, 6,8-H), 6.80 (d, J=9 Hz, 2H, 3',5'-H), 7.30 (d, J=9 Hz, 2H, 2',6'-H).

MS(rel. int.) : m/z 315 (12.59), 314 (62.51), 313 (37.54), 207 (20.29), 181 (15.85), 180 (70.12), 152 (37.55), 137 (27.49), 135 (12.48), 134 (100), 121 (37.91), and 119 (20.48).

Reaction of 2'-hydroxy-4,4'-dimethoxychalcone (XLV) with copper(II) acetate in the presence of perchloric acid

Copper(II) acetate (5.40 g, 28 mmol) was dissolved in acetic acid (80 ml) containing 70% perchloric acid (15 ml,168 mmol). 2'-Hydroxy-4,4'-dimethoxychalcone (XLV) (4.00 g, 14 mmol) was then added slowly to it with continuous shaking. The reaction mixture was left stirring at room temperature and the progress of the reaction was monitored by thin layer chromatography. T.l.c. examination of the reaction mixture even after ten days revealed no change. The contents were then heated on a water bath for eight hours. The reaction was worked up by pouring the contents into water and extracting the organic material with benzene. The organic layer was washed with aqueous sodium bicarbonate followed by water,

dried over anhydrous sodium sulphate and evaporated to give a crude solid (3.92 g) which was chromatographed over a silica gel column. Unreacted starting chalcone (1.75 g) was recovered when the petrol: benzene (3:2) was used as eluent. Elution of the column with petrol-benzene (1:4) afforded a light green solid which was crystallized from methanol as hexagonal flakes (0.940 g), m.p.93-4°C. This compound was characterized as 7,4'-dimethoxyflavanone (LI). A yellow solid eluted with benzene and crystallized from ether-ethyl acetate mixture (107 mg), m.p.173-4°C, was found identical in all respects to an authentic sample of I-2',II-2'-dihydroxy-I-4,II-4,I-4',II-4'-tetramethoxy-[I-β,II-3']-dihydrobichalcone (XLVI) (m.m.p., i.r., u.v., n.m.r. and mass). A gummy dark brown mixture of polymeric products (0.190 g) was obtained when the column was finally eluted with ethyl acetate.

7,4'-Dimethoxyflavanone (LI)

M.p. : 93-4°C

IR(KBr) : ν_{max} 2980, 2830, 1675, 1610, 1570, 1515, 1440, 1420, 1350, 1330, 1310, 1250, 1200, 1160, 1115, 1060, 1020, 990, 945, 880, 840, 815, 665, 640 and 625 cm^{-1}.

UV(EtOH) : λ_{max} 275 and 310 nm.

NMR($CDCl_3$) : δ 2.86 (mc, 2H, 3-H), 3.80 (s, 6H, 7,4'-OMe), 5.36 (dd, J_{trans}=11 Hz, J_{cis}=5 Hz, 1H, 2-H), 6.46 (d, J=2.5 Hz, 1H, 8-H), 6.56 (dd, J_1=2.5 Hz, J_2=9 Hz, 1H, 6-H), 6.90 (d, J=9 Hz, 2H, 3',5'-H), 7.40 (d, J=9 Hz, 2H, 2',6'-H), 7.84 (d, J=9 Hz, 1H, 5-H).

MS(rel. int.) : m/z 285 (8.75), 284 (42.59), 283 (22.49), 269 (9.13), 267 (9.78), 177 (10.27), 176 (3.54), 161 (2.80), 151 (20.48), 150 (10.67), 135 (12.57), 134 (100), 121 (42.49) and 119 (17.60).

Reaction of 2'-hydroxy-3,4,4'-trimethoxychalcone (XLVII) with copper(II) acetate in the presence of perchloric acid

To a solution of copper(II) acetate (6.11 g, 31.8 mmol) in acetic acid (100 ml) and perchloric acid (16.36 ml, 190.8 mmol), 2'-hydroxy-3,4,4'-trimethoxychalcone (5.00 g, 15.9 mmol) was added and the reaction mixture was stirred at room temperature for ten days. T.l.c. examination did not reveal any change and the contents were then heated on a water bath for eight hours. The reaction was worked up in the previously described manner. The organic material was extracted with ethyl acetate. The ethyl acetate contents were washed several times with aqueous sodium bicarbonate and water and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded a dark coloured gummy solid

(4.85 g) which was adsorbed on silica gel and column chromatography was performed. Column was eluted with petrol:benzene (1:1) to give unreacted 2'-hydroxy-3,4,4'-trimethoxychalcone (2.2 g). Elution of the column with benzene afforded a very light yellow solid which was crystallized from petrol:acetone mixture as light yellow crystals of 7,3',4'-trimethoxyflavanone (LII) (1.25 g), m.p.117-8°C. Further elution of the column with benzene:ethyl acetate (49:1) furnished a yellow solid, crystallized from alcohol-ether mixture (109 mg), m.p.155-6°C. This product was identified as I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-3']-dihydrobichalcone (XLVIII), on comparing the spectral data (i.r., u.v., n.m.r. and mass) with that of an authentic sample of XLVIII. Furthermore elution of the column with the same eluent afforded another bright yellow solid crystallized from ethyl acetate (300 mg), m.p.174-5°C. This compound was found identical in all respects to authentic sample of I-2',II-2'-dihydroxy-I-3,II-3,I-4,II-4,I-4',II-4'-hexamethoxy-[I-β,II-5']-dihydrobichalcone (XLIX) (m.m.p., i.r., u.v., n.m.r. and mass). Finally the column was eluted with ethyl acetate to give a mixture of polymeric products (0.4 g).

7,3',4'-Trimethoxyflavanone (LII)

M.p. : 117-8°C

IR(KBr) : ν_{max} 2980, 2930, 1670, 1600, 1560, 1510, 1410, 1345, 1270, 1230, 1215, 1190, 1170, 1140, 1120, 1070, 1060, 1025, 1010, 990, 930, 850, 815, 790, 760, 685 and 635 cm^{-1}.

UV(EtOH) : λ_{max} 234, 274 and 310 nm.

NMR($CDCl_3$) : δ 2.94 (mc, 2H, 3-H), 3.86 (s, 3H, 3'-OMe), 3.95 (s, 6H, 4,4'-OMe), 5.45 (dd, J_{trans}=11 Hz, J_{cis}=5 Hz, 1H, 2-H), 6.55 (d, J=3 Hz, 1H, 8-H), 6.64 (dd, J_1=9 Hz, J_2=3 Hz, 1H, 6-H), 7.04 (mc, 3H, 2',5',6'-H), 7.90 (d, J=9 Hz, 1H, 5-H).

MS(rel. int.) : m/z 314 (10.97), 313 (4.87), 299 (2.44), 191 (2.44), 177 (13.41), 165 (12.19), 164 (100), 152 (9.15), 151 (97.68), 150 (7.31), 149 (43.90), 137 (9.75), 135 (7.31), 122 (5.97), 121 (12.19) and 107 (7.31).

BIBLIOGRAPHY

1. R. Breslow, Quart. Rev. Chem. Soc., 1, 553 (1972).

2. J.H. Adams, P. Gupta, M.S. Khan and J.R. Lewis, J. Chem. Soc. Perk. Trans. I, 2173 (1977); L. Merlini and A. Zanarotti, J. Chem. Soc. Chem. Commun., 695 (1979).

3. T.A. Geissman, 'Chemistry of flavonoid compounds', Pergamon Press (1962) (a) p.468, (b) p.546 and 583, (c) p.72.

4. K. Venkataraman, in 'Progress in the chemistry of organic natural products', L. Zeichmeister (Ed.), Springer-Verlag, New York (1959); (a) p.2, (b) p.46.

5. C.H. Lea and P.A.T. Swoboda, Chem. and Ind., 1429 (1956); A.C. Mehta and T.R. Seshadri, J. Sci. Ind. Res., 18B, 24 (1959).

6. S.M. Kupchan, C.W. Sigel, R.J. Hemingway, J.R. Knox and M.S. Udayamurthy, Tetrahedron, 25, 1603 (1969).

7. S.P.S. Jagat, S. Singh, H.S. Garg, N.M. Khanna and M.M. Dhar, Phytochemistry, 15, 232 (1976).

8. J.B. Harborne, T.J. Mabry and H. Mabry, 'The flavonoids', Chapman and Hall, London (1975); (a) p.693, (b) p.79, (c) p.51.

9. H.D. Locksley, in 'Progress in the chemistry of natural products', L. Zeichmeister (Ed.), Springer-Verlag, New York (1973), p.207.

10. T.J. Mabry, K.R. Markham and M.B. Thomas, 'The systematic identification of flavonoids', Springer-Verlag, New York-Heidelberg (1970).

11. T.J. Batterham, 'NMR spectra of simple heterocycles', Wiley, New York (1973); p.385.

12. T.J. Mabry, J. Kagan and H. Roster, Monograph, 'Nuclear magnetic resonance analysis of flavonoids', Univ. of Texas Publication, No.6418 (1964).

13. J. Massicot and J.P. Marthe, Bull. Soc. Chim. Fr., 1962 (1962).

14. J.W. Clark-Lewis, L.M. Jackson and T.M. Spotswood, Aust. J. Chem., (a) 17, 632 (1964); (b) ibid., 31, 2059 (1968).

15. M. Okigawa, N. Kawano, W. Rahman and M.M. Dhar, Tetr. Lett., 4125 (1972); M. Okigawa, N.U. Khan, N. Kawano and W. Rahman, Chem. and Ind., 575 (1974); J. Chem. Soc., 1563 (1975).

16. A. Pelter, R. Warren, J.W. Usmani, R.H. Rizvi, M. Ilyas and W. Rahman, Experientia, 25, 350 (1969).

17. T.J. Batterham and R.J. Highet, Aust. J. Chem., 17, 428 (1964).

18. A.C. Waiss Jr., R.E. Lundin and D.J. Stern, Tetr. Lett., 513 (1964).

19. R.G. Wilson and D.H. William, J. Chem. Soc.(C), 2477 (1968).

20. D.G.I. Kingston, Tetrahedron, 27, 2691 (1971).

21. R.I. Reed and J.M. Wilson, J. Chem. Soc.(C), 5949 (1963).

22. A. Pelter, P. Staintor and M. Barber, J. Heterocyclic Chem., 2, 262 (1965).

23. H. Audier, Bull. Soc. Chim. Fr., 2892 (1966).

24. C. Van de Sande, J.W. Serum and M. Vandewalle, Org. Mass Spectrom., 6, 1333 (1972).

25. B.S. Joshi, V.N. Kamal and N. Vishwanathan, Phytochemistry, 9, 881 (1970).

26. J.B. Harborne, 'Comparative biochemistry of flavanoids', Academic Press, London (1967); p.251.

27. H. Grisebach and W. Barz, Naturwis., 56, 538 (1969).

28. H. Pacheco, Bull. Soc. Franc. Physiol. Vegetable, 15, 3 (1969).

29. A.J. Birch and F.W. Donovan, Aust. J. Chem., 6, 360 (1953).

30. H. Grisebach, Z. Natur., 12b, 227, 597 (1957); ibid., 13b, 335 (1958); ibid., 14b, 485 (1959).

31. T.A. Geissman and T. Swain, Chem. and Ind., 984 (1957).

32. H. Grisebach, Planta Med., 10, 385 (1962).

33. H. Grisebach and G. Brandner, Biochim. Biophys. Acta, 60, 51 (1962).

34. F. Kreuzaler and K. Hahlbrock, FEBS Letters, 28, 69 (1972).

35. H. Grisebach and L. Patschke, Z. Naturf., 16b, 645 (1961).

36. H. Grisebach and G. Brandner, Z. Naturf., 16b, 2 (1961).

37. H. Grisebach and W. Bilhuber, Z. Naturf., 22b, 746 (1967).

38. L. Patschke, W. Barz and H. Grisebach, Z. Naturf., 19b, 1110 (1964).

39. F.M. Dean, 'Naturally occurring oxygen ring compounds', Butterworth, London (1963); p.335.

40. E. Wong and E. Moustafa, Tetr. Lett., 3021 (1966).

41. H. Grisebach and W.D. Ollis, Experientia, 17, 4 (1961).

42. J. March, 'Advanced organic chemistry', McGraw-Hill, New York (1968); p.620.

43. G. Litkei and R. Bognar, Acta Chim. Hung., 77, 93 (1973).

44. J. Algar and J.P. Flynn, Proc. Roy. Irish Acad., 42b, 1 (1934).

45. T. Oyamada, J. Chem. Soc.(Japan), 55, 1256 (1934).

46. A.J. Birch in 'Chemical taxonomy', T. Swain (Ed.), Butterworth, London (1963); chapter 6.

47. J.D. Bu'Lock, 'Biosynthesis of natural products', McGraw-Hill, New York (1965); (a) p.90, (b) p.86.

48. A. Pelter, J. Bradshaw and R.F. Warren, Phytochemistry, 10, 835 (1971).

49. D.G. Roux and D. Ferreira, Phytochemistry, 13, 2039 (1974).

50. E.W. Underhill, J.E. Watkin and A.C. Neish, Can. J. Biochem. Physiol., 35, 219 (1957).

51. E. Wong, Chem. and Ind., 1985 (1954).

52. J.P. Van Der Merwe, D. Ferreira, E.V. Brandt and D.G. Roux, J. Chem. Soc. Chem. Commun., 521 (1972).

53. F. Du R. Volsteedt, G.J.H. Rall and D.G. Roux, Tetr. Lett., 1001 (1973).

54. E. Wong, Phytochemistry, 6, 1227 (1967).

55. P. Monitto, 'Biosynthesis of natural products', Ellis Horwood Ltd. Publishers (1981); p.410.

56. J.W. Clark-Lewis and D.C. Skingle, Aust. J. Chem., 20, 2169 (1967).

57. J.W. Clark-Lewis and R.W. Jamison, Aust. J. Chem., 21, 2247 (1968).

58. L. Jurd, Chem. and Ind., 2175 (1967); Tetrahedron, 23, 1057 (1967).

59. E. Haslam, Phytochemistry, 16, 1625 (1977).

60. W. Baker, A.C.M. Finch, W.D. Ollis and K.W. Robinson, J. Chem. Soc., 1477 (1963).

61. K.P. Mathai and S. Sethna, J. Ind. Chem. Soc., 41, 347 (1964); ibid., 44, 148 (1969).

62. M.R. Parthasarthy, K.R. Ranganathan and D.K. Sharma, Indian J. Chem., 15B, 942 (1977).

63. M.R. Parthasarthy and S. Gupta, Indian J. Chem., 23B, 227 (1984).

64. K. Nakazawa, Chem. Pharm. Bull.(Japan), 7, 748 (1959) and references therein; 10, 1032 (1962); 16, 2503 (1968).

65. S. Ahmad and S. Razaq, Tetr. Lett., 4633 (1971); S. Moriyama, M. Okigawa and N. Kawano, ibid., 2105 (1972).

66. J.B. Harborne and T.J. Mabry, 'The flavonoids: Advances in Research', Chapman and Hall, London (1982).

67. R.J. Molyneux, A.C. Waiss and W.F. Haddon, Tetrahedron, 26, 1409 (1970).

68. M. Kamil, M. Ilyas, W. Rahman, N. Hasaka, M. Okigawa and N. Kawano, Chem. and Ind., 160 (1977).

69. A.I. Kuhnle, J.J. Windle and A.C. Waiss, Jr., J. Chem. Soc.(B), 613 (1969).

70. S. Natarajan, V.V.S. Murti and T.R. Seshadri, Ind. J. Chem., 9, 383 (1971).

71. N. Chandramouli, S. Natarajan, A.K. Jhinga, T.R. Seshadri and V.V.S. Murti, Ind. J. Chem., 16B, 922 (1978).

72. D.N. Dhar, 'The chemistry of chalcones and related compounds', John, Wiley and Sons, New York (1981).

73. R.S. Verma and M. Verma, Synth. Commun., 12, 927 (1982).

74. B. Jackson, H.D. Locksley, F. Scheinmann and W.A. Wolstenholme, J. Chem. Soc.(C), 3791 (1971).

75. J.W. Cooper, in 'Spectroscopic techniques for organic chemists', John Wiley and Sons, New York (1980).

76. S.M. Ali, Unpublished results.

77. B.R. Borwn in 'Oxidative coupling of phenols', W.I. Taylor and A.R. Battersby (Ed.), Marcel Dekker, Inc., New York (1967); p.197.

78. H. Dugas and C. Penney, 'Bio-organic chemistry', Springer-Verlag, New York (1981); p.329.

79. R. Breslow and C. McAllister, J. Amer. Chem. Soc., 93, 7096 (1971).

80. G.J. Llyod and B.S. Copperman, J. Amer. Chem. Soc., 93, 4883 (1971).

81. J.M. Allen, K.M. Johnston, J.F. Jones and R.G. Shotter, Tetrahedron, 33, 2083 (1977).

82. T.C. Jempty, L.L. Miller and Y. Mazur, J. Org. Chem., 45, 749 (1980).

83. S. Tobinaga and E. Kotani, J. Amer. Chem. Soc., 94, 309 (1972).

84. T.A. Geissman, J. Amer. Chem. Soc., 697 (1946).

LIST OF PUBLICATIONS

1. Importance of solid support in organic synthesis, a novel reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone with silica bound ferric chloride,
Veena Manchanda and Nizam-Ud-Din Khan, Chem. and Ind., 127 (1985).

2. Dehydrogenation of flavonoids with the iodine-dimethyl sulphoxide-sulphuric acid reagent system,
Waseem Fatma, Jawaid Iqbal, Veena Manchanda, Waris A. Shaida, and Wasiur Rahman, J. Chem. Research(S), 298; (M), 2656(1984).

3. Oxidation of 2,3-xylenol with iron(III) ion,
Veena Manchanda and Nizam-Ud-Din Khan, Proc. of IInd Annual Conference of Indian Council of Chemists, Srinagar, Nov.6-8, 1982, OP-65.

4. Copper(II) ion promoted oxidation of 2,3-xylenol and its biological importance,
Veena Manchanda and Nizam-Ud-Din Khan, Proc. of IVth Annual Conference of Indian Council of Chemists, Gorakhpur, Dec.30-31, 1984 and Jan.1, 1985, OO-27.

5. Metal ion oxidation of 2,3-xylenol,
Veena Manchanda and Nizam-Ud-Din Khan (under preparation).

6. Silica bound ferric chloride oxidation of 2'-hydroxy-4,4',6'-trimethoxychalcone,
Veena Manchanda and Nizam-Ud-Din Khan (under preparation).

7. Reaction of 2'-hydroxychalcones with $Cu(OAc)_2$-$HClO_4$-HOAc reagent system,
Veena Manchanda and Nizam-Ud-Din Khan (under preparation).

8. Reaction of resorcinol derived chalcones with silica bound ferric chloride,
Veena Manchanda and Nizam-Ud-Din Khan (under preparation).